

National Center for Toxicological Research Annual Report Research Accomplishments and Plans



FY 2008 - FY 2009

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Preface

The National Center for Toxicological Research (NCTR) is an important research component of the U.S. Food and Drug Administration (FDA) that plays a critical role in FDA's and the Department of Health and Human Services' (DHHS) mission to promote and protect public health. The vision of NCTR is to be an internationally recognized FDA research center that provides innovative, vital scientific technology, training, and technical expertise to improve public health. NCTR—in partnership with researchers from government, academia, and industry—develops, refines, and applies current and emerging technologies to improve safety evaluations of FDA-regulated products. NCTR fosters national and international collaborations to improve and protect public health and enhance the quality of life for the American people. The Center—located in Jefferson, Arkansas, approximately 30 miles south of Little Rock—is co-located with the Office of Regulatory Affairs' Arkansas Regional Laboratory.

NCTR conducts FDA mission-critical, peer-reviewed, critical path (translational) research targeted to developing a scientifically sound basis for regulatory decisions and reducing risks associated with FDA-regulated products. This research is aimed at evaluating the biological effects of potentially toxic chemicals or microorganisms, defining the complex mechanisms that govern their toxicity, understanding critical biological events in the expression of toxicity, and developing methods to improve assessment of human exposure, susceptibility, and risk. NCTR's research efforts are primarily directed at supporting FDA's Strategic Goal framework by implementing the objectives of FDA's Strategic Goal 1 (Strengthen FDA for Today and Tomorrow), FDA's Strategic Goal 2 (Improve Patient and Consumer Safety), FDA's Strategic Goal 3 (Increase Access to New Medical and Food Products), and FDA's Strategic Goal 4 (Improve the Quality and Safety of Manufactured Products and the Supply Chain).

Customized bioassessment of chemicals of vital interest to FDA involves the coordination of expertise in the areas of biochemical and molecular markers of safety and toxicity, neurotoxicology, microbiology, chemistry, genetic or reproductive/developmental toxicology, and systems-biology assessments for characterizing biomarkers for an individual's susceptibility to toxicants, disease risk, and health status. Using its strengths in methods development, statistics, analytical chemistry, and spectroscopy, NCTR has developed and is standardizing technologies, such as genomics, proteomics, metabonomics, and nanotechnology, to identify and characterize early biomarkers of toxicity using quantitative risk-assessment methods. In addition, NCTR is using toxicoinformatics (data collection, interpretation, and storage of information about gene, protein, and metabolite expression) to manage and integrate data from these new technologies with traditional toxicological data to provide a basis for better predictive toxicology. Application of these new tools in animal surrogates will provide mechanistic biomarkers that will have more relevance for extrapolation of risk to humans, provide a better understanding of the present models used to assess risk in humans, and direct the development of more useful surrogate models that will increase our understanding of toxic responses in humans including a focus on women's health

issues. The training of scientists within and outside FDA concerning these cutting-edge concepts, approaches, and techniques is a major objective of NCTR.

A significant contribution to our research accomplishments is the benefit gained by sharing knowledge through collaborations with scientific staff in all disciplines from other FDA Centers as well as in other government agencies, academia, and industry. One such example is the use of ArrayTrack™, a software tool developed at NCTR to store, analyze, and interpret DNA microarray data. This tool is being used by several FDA regulatory Centers in assessing pharmacogenomic and other omics data voluntarily submitted by the regulated industry. This collaboration is one that identifies FDA as a catalyst in the development of new standards that will facilitate drug development for the promotion and protection of public health and provide a pathway to personalized nutrition and medicine. To facilitate the accomplishment of these goals, a new Division of Personalized Nutrition and Medicine has been established and a new NCTR/FDA Bio-Imaging Center is under development to provide noninvasive, translatable biomarkers for safety assessment. In addition to methods and standards development, NCTR conducts safety assessment of compounds nominated to FDA for evaluation under an agreement with the National Institute of Environmental Health Sciences/National Toxicology Program.

/s/

William Slikker, Jr., Ph.D.

Director, NCTR

Vision/Mission

Vision

NCTR is an internationally recognized FDA research center that provides innovative and vital scientific technology, training, and technical expertise to improve public health. NCTR—in partnership with researchers from government, academia, and industry—develops, refines, and applies current and emerging technologies to improve safety evaluations of FDA-regulated products. NCTR fosters national and international collaborations to improve and protect public health and enhance the quality of life for the American people.

Mission

NCTR conducts peer-reviewed scientific research in support of the FDA mission and provides expert technical advice and training that enables FDA to make sound science-based regulatory decisions and improve the health of the American people. The research at NCTR supports FDA's goals: 1) to understand critical biological events in the expression of toxicity, 2) to develop and characterize methods, and incorporate new technologies to improve the assessment of human exposure, susceptibility, and risk, and 3) to increase the understanding of the interaction between genetics, metabolism, and nutrition.

NCTR is dedicated to supporting the FDA mission to protect and promote public health by:

- providing innovative and interdisciplinary research that promotes personal and public health
- developing novel translational research approaches to provide FDA/DHHS with sound scientific infrastructure and multidisciplinary scientific expertise targeted towards addressing critical agency, department, and public-health needs such as personalized nutrition and medicine, bioimaging, systems biology, bioinformatics, nanotechnology, food protection technologies, and biomarker development
- engaging with scientists across FDA and other government agencies, industry, and academia in cooperative learning to strengthen the scientific foundations vital to developing sound regulatory policy and leveraging resources to promote the international standardization and global harmonization of regulatory science
- participating in or leading national and international consortia for the development of harmonized standards for technologies and methods in risk assessment and for personal and public health

NCTR Strategic Plan

NCTR's Strategic Plan sets forth our long-term strategic goals and objectives. The plan also details specific actions we are committed to taking as we carry out our mission of promoting and protecting the public health.

This Strategic Plan charts NCTR's course for the future, focusing on four strategic goals: 1) strengthening the FDA, 2) improving the safety of patients and consumers, 3) increasing access to new medical and food products, and 4) improving the safety and quality of manufactured products and the supply chain. Each of these goals represents a fundamental public-health task that is crucial to fulfilling our mission.

To accomplish its mission, NCTR has established five strategic goals:

- Goal 1: Advance scientific approaches and tools to promote personalized nutrition and medicine for the public
- Goal 2: Develop science-based best-practice standards, guidance, and tools to incorporate toxicological advancements that improve the regulatory process.
- Goal 3: Conduct research and develop strategic technologies to protect the food supply
- Goal 4: Conduct bioinformatics research and development in support of FDA's regulatory mission
- Goal 5: Strengthen and improve scientific and human capital management and expand training and outreach to to retain and train scientific experts critical to address FDA's scientific needs

The NCTR Strategic Plan is on the FDA Web site at

<http://www.fda.gov/AboutFDA/CentersOffices/NCTR/NCTRStrategicPlan/default.htm>.

Research Structure

Established by executive order in 1971, the National Center for Toxicological Research (NCTR) is internationally recognized for the conduct of scientific research that supports the FDA mission to bring safe and efficacious products to market and reduce the use of adverse health effects.

The divisions include interdisciplinary teams of scientific experts that conduct fundamental and innovative laboratory research that translates knowledge and technology into processes that improve the safety assessment of FDA-regulated products and reduces the risk of adverse effects from products on the market. NCTR science is structured into divisions having specific disciplines that work as cross-functional teams to address agency concerns in Food Protection Plan, Modernizing Science, and Product Safety.

- Division of Biochemical Toxicology
- Division of Genetic and Reproductive Toxicology
- Division of Microbiology
- Division of Neurotoxicology
- Division of Personalized Nutrition and Medicine
- Division of Systems Toxicology
- Division of Veterinary Services

Science Advisory Board

Function

The Science Advisory Board (SAB) advises the NCTR Director in establishing, implementing, and evaluating the scientific-research programs conducted at NCTR. NCTR conducts innovative scientific research that assists the FDA Commissioner in fulfilling the FDA's regulatory responsibilities. Through Site-Visit reviews and annual meetings, NCTR's SAB provides an extra-agency scientific program review of the research programs at NCTR. The recommendations of the SAB are critical to the scientific rigor of the studies conducted at NCTR. Members of the SAB and the Chair are selected by the FDA Commissioner or designee from among leading authorities in fields related to toxicological research.

FY 2008 Accomplishments

A Site-Visit Subcommittee of the NCTR SAB performed an in-depth site-visit review of the research programs within the Division of Biochemical Toxicology on April 29-30, 2008. The site-visit team was led by Dr. James Popp, SAB Board Chair, and included subject matters expert consultants from academia, industry, and the National Institutes of Health. Representatives from the FDA Centers participated in the review. The Division presented results from, and future plans on, studies evaluating the hazards of food, drugs, and cosmetics. In a report to the SAB, the Site-Visit Subcommittee complimented the Division Director, Dr. Fred Beland, on the high quality of research being conducted within the Division and recommended that: 1) internal dosimetry be included on all bioassays, 2) pharmacokinetics and pharmacodynamics of melamine and cyanuric acid in rodents be assessed before planning toxicity studies in pigs, and 3) a scanning electron microscope be utilized to evaluate nanoparticles *in vivo*.

The full NCTR SAB meeting was held at NCTR on August 12-13, 2008. The meeting included presentations on ongoing-research activities from each of the NCTR Divisions. Each Division Director updated the SAB on the major research findings of the past year, the important implications of the findings for FDA, and major scientific issues with current research.

The SAB was also asked to accept Site-Visit Subcommittee reports from site visits of the Microbiology and Biochemical Toxicology divisions. Following acceptance of the reports, Division Directors of the two divisions responded to the recommendations made by the Site-Visit Subcommittee.

The NCTR Director provided an overview of centerwide scientific endeavors and discussed the alignment and strategic focus of NCTR. The overview included a discussion of the current and new research programs at the Center, including the Food Protection Plan, Critical Path, Imaging, Nutrition and Obesity, and Nanotechnology.

SAB Membership Roster

Chair:

James A. Popp, D.V.M., Ph.D.

Term: 07/31/06-06/30/10

Expertise: Toxicology

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Consumer Representative—Vacant

NCTR Synergistic Research Through Outreach and Collaboration

Throughout its history, NCTR has actively sought and participated in collaborative, cooperative partnerships with other scientific and regulatory organizations. These opportunities to leverage resources, both public and private, enable NCTR to address questions of common concern to both FDA and the collaborating agency. These partnerships have led to substantial research advances that have resulted in significant improvements in long-term public health, such as regulatory guidances, mechanistic understanding, and advanced methodology.

Interagency Agreements

Interagency Agreements (IAGs) are formal financial partnerships with other government agencies. NCTR has been fortunate in establishing IAGs with other government agencies to conduct research on problems of common interest to the FDA and the collaborating agency. The most significant, in terms of size, is the IAG between NCTR/FDA and the National Institute of Environmental Health Sciences (NIEHS).

National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP)

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In 1992, the Food and Drug Administration (FDA) entered into an IAG with NIEHS. The NIEHS National Toxicology Program (NTP) conducts toxicology studies at the request of the FDA and other federal agencies. The IAG is an instrument that allows chemicals nominated to the NTP to be studied for toxicity using the unique resources and facilities at NCTR. The research conducted under the IAG provides FDA the ability to better assess to study design input and initial data on the safety of FDA-regulated products.

The 1992 agreement provided support for five FDA priority chemical/agent NTP nominations. The agreement has expanded to allow continued collaborative toxicity testing on compounds of interest to the FDA and NTP. The IAG has led to the investigation of the mechanism of action and toxicity assessment of many classes of chemicals including cosmetics, endocrine disruptor compounds, food contaminants, food cooking byproducts, dietary supplements, drugs, and anesthetics. In response to experimental design needs for compounds studied under the IAG, the IAG supported the development of the Phototoxicity Research and Testing Laboratory (NTP Center for Phototoxicology) and NCTR/ORA Nanotechnology Core Facility.

All toxicology studies conducted under the IAG are designed with input from FDA regulatory scientists, NCTR and NIEHS scientists, scientists from other agencies, and invited subject matter experts. The IAG utilizes resources from public funds and

exceptional scientific expertise to provide the best possible assessment of product safety through toxicological studies.

Toxicological studies on numerous compounds have been supported since 1992. Many of the compounds are listed below with the nominating center in parenthesis.

- α and β Hydroxy Acids dermal (CFSAN)
- Acrylamide (CFSAN)
- AIDS Therapeutics (Zidovudine, Nelfinavir, Nevirapine, Lamivudine)
- *Aloe vera* oral
- *Aloe vera* dermal
- Bisphenol A (CFSAN)
- Bitter Orange, *Citrus aurantium* (CFSAN)
- Chloral Hydrate (CFSAN)
- Di-(2-ethylhexyl)phthalate (CBER, CDRH)
- Ethinyl Estradiol (CDER)
- Fumonisin B1 (CFSAN)
- Furan (CFSAN)
- Genistein (CFSAN)
- Glucosamine/Chondroitin (CFSAN)
- Ketamine (CDER)
- Malachite Green (CVM)
- Melamine + Cyanuric Acid (CVM)
- Nanoscale Silver (FDA)
- Nonylphenol (CDER)
- Permanent Makeup Pigments (CFSAN)
- Retinyl Palmitate dermal (CFSAN)
- Riddelliine (CFSAN)
- Urethane/Ethanol (CFSAN)
- Usnic Acid, Usnea Lichen (CFSAN)

The NIEHS/NTP IAG currently supports the NCTR research projects include listed below.

- Furan—Determination of Carcinogenic Mechanisms and Low-Dose Carcinogenesis in Rats
- Acrylamide—Developmental Neurotoxicity Assessment in Rats
- Bitter Orange (*Citrus aurantium*)—Developmental and physiological toxicity in Rats
- Bisphenol A—Determination of the Pharmacokinetics in rats and nonhuman primates, Physiologically Based Pharmacokinetics (PBPK) Modeling, and Subchronic Toxicity in Rodents
- Di(2-ethylhexyl)phthalate (DEHP)—Toxicokinetics in Neonatal Male Rhesus Monkeys Following Intravenous and Oral Dosing
- Melamine and Cyanuric Acid—Toxicity Studies and Biomarker Identification in Rodents and Rabbits
- Retinyl Palmitate—Effect of Topically Applied Skin Creams Containing Retinyl Palmitate on the Photocarcinogenicity of Simulated-Solar Light (SSL) in SKH-1 Mice
- Acrylamide—Genotoxicity and Carcinogenicity of Acrylamide and its Metabolite, Glycidamide, in Rodents (Range-Finding, Subchronic, Two-Year Chronic Carcinogenicity Studies)
- Ketamine—NMDA Antagonist/GABA Agonist-Induced Cell Death in the Developing Rat Brain
- AIDS Therapeutics—Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmission of HIV
- Nanoscale Oxides—Skin Penetration and Phototoxicity of Nanoscale Oxides of Titanium and Zinc, and Quantum Dots

- Nanoscale Silver—Pharmacokinetics, Tissue Distribution, and Subchronic Toxicity in Rats
- Usnic acid, *Usnea Barbata*—Toxicity Studies in Fischer 344 Rats and B6C3F1 Mice
- Glucosamine and Chondroitin Sulfate—Subchronic Toxicity in Fischer 344 Rats and Diabetic Goto-Kakizaki Rats
- Permanent Makeup Inks—Determination of the Immunogenicity of Inks and their Components
- AIDS Therapeutics: Toxicity Studies of Combinations in p53 (+/-) Haploinsufficient Transgenic Mice

In addition to the IAG with NIEHS/NTP, NCTR has received support from other government agencies. The IAGs currently supporting NCTR research projects include those listed below.

Centers for Disease Control—Mouse Lymphoma Assay

Evaluation of the Ability of the Agar and Microwell Versions of the Mouse Lymphoma Assay (MLA) to Optimally Detect the Mutagenic Potential and Potency of Complex Chemical Mixtures

National Institute of Child Health and Human Development (NICHD)—Gaseous Anesthetics

Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate

National Institute of Child Health and Human Development (NICHD)—Ketamine

Assessment of Ketamine in the Developing Nonhuman Primate

National Institute of Child Health and Human Development (NICHD)—Methylphenidate

Evaluation of Growth and Pubertal Development in Male Rhesus Monkeys (*Macaca Mulatta*) Chronically Exposed to Methylphenidate Hydrochloride (MPH)

National Institutes of Health/National Institute of Child Health and Human Development (NIH/NICHD)—Methylphenidate in Rhesus Monkey and Big Blue[®] Mice

Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys (*Macaca mulatta*)

Collaborative Research and Development Agreements

NCTR actively pursues and maintains partnerships with nongovernmental organizations, nonprofit organizations and private companies through Collaborative Research and Development Agreements (CRADAs).

Astra Charnwood

Evaluation of Changes in Gene Expression in the Brain Associated with Normal Development and the Behavioral Toxicity Caused by Developmental Exposure to the N-Methyl-D-Aspartate-(NMDA) Receptor Antagonists, Sodium Channel Blockers, and Combinations

BG Medicine, Inc.

Liver-Toxicity Biomarkers Study: Phase 1, Entacapone and Tolcapone

Boehringer Ingelheim Pharmaceuticals, Inc.

Pramipexole: Thirty-Week Toxicity Study in Juvenile Rhesus Monkeys Followed by a Twelve-Week Recovery Period: Use of a Nonhuman Primate Model for Studying the Consequences of Long-Term Dopaminergic-Receptor Stimulation on Complex Brain Functions Using the NCTR Operant Test Battery

CIIT Centers for Health Research

Evaluating the Utility of ACB-PCR in Dose-Response Assessment and Mode-of-Action Evaluation

Pfizer, Inc.

Cognitive Assessments of Several Psychotropic Compounds Using the NCTR Operant Test Battery (OTB)

Pfizer, Inc.

Evaluation of the Mechanisms of Inactivation and Degradation of Third-Generation Cephalosporins by the Bovine-Intestinal Microflora

SAS Institutes, Inc.

Development of ArrayTrack™ Modules to Link Functionality of ArrayTrack™ with SAS Scientific Discovery Solutions (SDS)

University of Arkansas—Fayetteville

Wireless Deep-Brain Stimulation in Nonhuman Primates with MPTP-Induced Parkinson's Disease

University of Arkansas for Medical Sciences

Ketamine Pharmacokinetics in Children

University of Arkansas for Medical Sciences

Novel Studies on Sites-of-Action and Mechanisms in Chronic Balance Dysfunction

University of Illinois

Phytoestrogens and Aging: Dose, Timing, and Tissue

University of Maryland

Development of a PBPK/PD Model for Acrylamide

Office of Women's Health

The Office of Women's Health (OWH) Science Program was started in 1994 to fund research projects that provide a foundation for the development of sound policies and regulations that enhance the health of women. This program has provided support for approximately 30 women's health research studies at NCTR. These studies have investigated several important women's health issues including: 1) importance of sex differences in drug metabolism, 2) comparative effectiveness of chemotherapeutic medicines, and 3) understanding the biological changes that cause lupus. The OWH Science Program also provided funding for NCTR's Endocrine Disruptor Knowledge Base, which is been extensively utilized to determine a compound's estrogenic activity and has served as the prototype for newer bioinformatics tools, such as ArrayTrack™. In 2008, NCTR formed a Women's Health Research Group and seminar series to promote and coordinate research in women's health within the Center. The Women's Health Research Group runs an active and innovative research program that focuses on 1) understanding the molecular basis of drug efficacy and safety and 2) how genetics, sex, diet, and other environmental factors influence drug efficacy and safety.

The NCTR projects listed in this section were supported by OWH in FY 2008 or have been approved for support in FY 2009.

Assessment of Effects and Metabolism of Synthetic Azo Colorants Used in Women's Cosmetics on Human Skin Microbiota

Evaluating the Effects of Over-the-Counter Skin Products, such as Sunscreen, on the Absorption of Dermally Applied Estradiol, in an *In Vitro* and *In Vivo* Model

Gene-Expression Responses of Estrogen-Primed Vaginal-Epithelial Cells After Contact with *Lactobacillus* Rhamnosus GR-1, *Lactobacillus reuteri* RC-14, and the Pathogenic Fungus, *Candida albicans*

Genotyping of Transporter Genes Associated with Gender Differences and Promoter Methylation of UGT1A1 in Human Liver: A Means of Assessing Safety and Toxicity of Chemotherapeutic Drugs

Mechanisms of Gender Differences in Aspirin Effects: Metabolizing Enzymes and Therapeutic Targets

Sex differences in Systemic Lupus Erythematosus (SLE): Effects of a Single Nucleotide Polymorphism (SNP) in the Prolactin (PRL) Gene on Individual Response to Prasterone Therapy

Systems-Biology Approach to Evaluate Sex Differences in the Heart of a Rat Model

Division of Biochemical Toxicology Summary of Activities

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Introduction

The Division of Biochemical Toxicology conducts fundamental and applied research specifically designed to define the biological mechanisms of action underlying the toxicity of products regulated by, or of interest to, the Centers of the Food and Drug Administration (FDA). This research centers on quantifying the toxicities and carcinogenic risks associated with specific chemicals and gene-nutrient interactions and the introduction of new techniques to assess toxicities and carcinogenic risks. The risk-assessment research is firmly rooted in mechanistic studies focused on the understanding of toxicological endpoints, an approach that allows greater confidence in the subsequent risk assessments. Research within the Division capitalizes on scientific knowledge in the areas of biochemistry, organic chemistry, analytical chemistry, cellular and molecular biology, nutritional biochemistry, toxicology, phototoxicology, and pharmacology.

FY 2008 Accomplishments

A major emphasis within the Division continues to be conducting research on compounds nominated by FDA for evaluation by the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP). This focus reflects NCTR's superb animal facilities supported by a multidisciplinary staff of scientists with strong mechanistic-research experience, which allows subchronic and chronic toxicological assessments to be conducted in a rigorous manner to address FDA's needs. These studies currently serve as the benchmark by which toxicological assessments are made by FDA and other federal agencies. In addition to providing basic information on toxicological endpoints, such as cancer, these experiments form the basis for mechanistic studies to ascertain if the response detected in the experimental model is pertinent to humans.

During FY 2008, draft pathology reports were completed for chronic bioassays on acrylamide, a carcinogen found in many baked and fried foods, which was nominated to the NTP by the Center for Food Safety and Applied Nutrition (CFSAN). Draft pathology reports were also completed on two-year chronic bioassays of glycidamide, a genotoxic metabolite of acrylamide. In addition, draft pathology reports were completed on bioassays in which newborn mice were dosed with acrylamide and glycidamide. The goal of this latter study was to determine if infants are particularly susceptible to the carcinogenic properties of acrylamide and its metabolite glycidamide.

During FY 2008, draft pathology reports were also completed on bioassays on *Aloe vera*, a widely used dietary supplement. In addition, a manuscript was published describing the effects of whole-leaf extracts of *Aloe vera* on the production of short-chain fatty acids by intestinal bacteria.

A major emphasis within the Division is elucidating potential toxicities associated with endocrine-disrupting chemicals. During FY 2008, final NTP technical reports were published on the toxicology, carcinogenesis, and multigenerational reproductive studies on genistein, a component of soy. In addition, manuscripts were submitted or published describing the effects of ethinyl estradiol on bone morphology and on comparing the multigenerational effects of genistein and ethinyl estradiol, including their effects on the mammary gland.

In response to a nomination by the Center for Biologics Evaluation and Research (CBER), and supported by the Center for Devices and Radiological Health (CDRH), Division investigators continued studies on the toxicokinetics of intravenous and oral di(2-ethylhexyl)phthalate (DEHP) (present in a variety of polyvinylchloride medical devices) in neonatal male rhesus monkeys, as a prelude to a possible subchronic toxicity study. These experiments are intended to model the exposure of male infants in a neonatal intensive care unit (NICU), which is the human population identified as being at the highest risk of DEHP-induced reproductive toxicity.

In other studies, high-performance liquid chromatography (HPLC) tandem mass-spectrometry methods were developed to detect and quantify DNA adducts from pyrrolizidine alkaloids, which are hepatotoxic and tumorigenic phytochemicals present in herbal products, including herbal dietary supplements sold in the United States.

An area of concern to FDA, in particular CFSAN, is the potential toxicity of cosmetic ingredients due to their interaction with light. To address this concern, NCTR, in collaboration with NIEHS/NTP, established the NCTR Center for Phototoxicology within the Division. During FY 2008, the final NTP technical report on photocarcinogenesis studies of *Aloe vera* was published. In addition, draft manuscripts were prepared describing the experiments investigating the dermal penetration of nanoscale titanium dioxide, a component of certain sunscreens and other cosmetics, in mice and mini-pigs.

Antiretroviral drugs are being used to prevent the mother-to-child transmission of human immunodeficiency virus (HIV) type-1, the virus responsible for AIDS. While effective in preventing viral transmission, the long-term consequences of perinatal exposure to these drugs are presently unknown. During FY 2008, draft pathology reports were completed on bioassays in which antiretroviral drugs were administered transplacentally to mice. In addition, bioassays were continued on studies in which the drugs were administered transplacentally and neonatally. In further studies, Division investigators published data describing the effects of antiretroviral drugs on cell-cycle kinetics.

In FY 2008, chemists in the Division designed studies to investigate the toxicities of melamine and cyanuric acid, chemicals contaminating pet food and, more recently, infant formula.

During FY 2008, Division investigators collaborated with scientists at the National Center for Food Safety and Technology (NCFST) to investigate the stability of ricin and abrin biological activity in several foods (infant formula, fruit juices, and yogurt) as a function of time and temperature. These studies led to the development of a sensitive enzyme-activity assay method for detecting the intrinsic 28S rRNA-specific adenosine-glycosidase activity shared by all ribosome-inactivating protein toxins.

A strong emphasis within the Division has been to determine whether epigenetic changes induced by carcinogens, and found in tumors, play a causative role in carcinogenesis or are merely a consequence of the transformed state. During FY 2008, Division investigators published manuscripts describing the role of microRNAs in the epigenetic alterations induced by both genotoxic and nongenotoxic carcinogens.

FY 2009 Plans

In FY 2009, Division investigators will complete NTP reports on the transplacental carcinogenicity of antiretrovirals drugs. Draft final reports will be prepared on chronic two-year bioassays of *Aloe vera* and acrylamide, and on the carcinogenicity of acrylamide and glycidamide in the newborn-mouse assay. Chronic studies will continue to determine the effects of transplacental and neonatal exposure to antiretroviral drugs. Mechanistic studies on acrylamide and glycidamide, including toxicokinetics, DNA and hemoglobin adduct dosimetry, and *in vivo* mutagenesis assays, will be combined with the results from the two-year chronic bioassay to develop a comprehensive risk assessment on acrylamide. Studies to assess the pharmacokinetics and toxicities of the food contaminant furan will be initiated. This will include a comprehensive two-year chronic bioassay. Experiments will be initiated to determine the toxicities associated with exposure to nanoscale silver particles.

Investigators associated with the NCTR Center for Phototoxicology will complete the final NTP report on the photocarcinogenicity of retinyl palmitate. Studies will be initiated to investigate the toxicities of topically applied triclosan, a broad-spectrum antimicrobial agent present in a wide variety of antibacterial soaps, deodorants, toothpastes, cosmetics, fabrics, plastics, and other products.

Investigations will continue to determine the pharmacokinetics and testicular toxicity of intravenously administered DEHP in neonatal rhesus monkeys and rats. These experiments will indicate if this plasticizer poses an undue risk to infants. Experiments will also be initiated to investigate the effects of Bisphenol A, a chemical used primarily to make plastics, especially with regard to developmental exposures.

Division investigators will conduct *in vivo* studies to evaluate the toxicities of melamine in combination with cyanuric acid. Division personnel will continue collaborations with investigators at the NCFST to measure thermodynamic constants for the thermal inactivation of bioterrorism agents, such as ricin and abrin, under conditions found in

foods and to compare the potencies of detergents and chemical sanitizing agents to inactivate or eliminate these bioterrorism agents that contaminate food-contact surfaces.

Contribution to FDA's Strategic Goals

The research conducted by the Division of Biochemical Toxicology contributes primarily to FDA Strategic Goals 2 and 4.

FDA Strategic Goal 2 (Improve Patient and Consumer Safety)

Division investigators are conducting studies to assess the toxicities associated with exposure to melamine and cyanuric acid, contaminants that have been found in certain food products.

Division investigators have developed new techniques that have improved the scientific capabilities of the agency. These include HPLC coupled with tandem mass-spectrometric methods to assess pharmacokinetic and toxicokinetic parameters of chemicals and drugs of interest to FDA and the introduction of new techniques for assessing the phototoxicity of chemicals.

FDA Strategic Goal 4 (Improve the Quality and Safety of Manufactured Products and the Supply Chain)

A major emphasis of the Division's research is to ensure the safety of food products. For example, ongoing assessments include acrylamide, a known rodent carcinogen, and a neurotoxicant that was recently identified in baked and fried starchy foods, notably french fries, potato chips, bread, coffee, and many other consumer food products. Evaluations are also being conducted on *Aloe vera*, a natural product incorporated into dietary supplements. As part of the Division's efforts to ensure the safety of foods, assays are being developed and applied to detect the biological activities of potential bioterrorism agents, for example ricin and abrin, in various food products. The Division also emphasizes toxicological assessments of chemicals found in cosmetic products. These chemicals include *Aloe vera*, retinyl palmitate, triclosan, and nanoparticles.

Division of Genetic and Reproductive Toxicology Summary of Activities

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Introduction

The Division of Genetic and Reproductive Toxicology (DGRT) conducts basic and applied research to address specific high-priority issues related to the induction of genetic damage. Division research is directed toward developing and validating new methods or improving existing methods for the identification of potentially hazardous food additives, human and animal drugs, biological therapies, and medical devices. In collaboration with other FDA scientists, DGRT utilizes the methodologies it develops to understand the potential toxicity of specific high-priority drugs, dietary supplements, and other agents.

As experts in the field of genetic toxicology, scientists in DGRT are actively involved in national and international efforts to harmonize the conduct of genetic-toxicology tests and to improve their interpretation and use for regulatory decision making. DGRT scientists frequently provide expert advice to the FDA Centers, other government agencies, academia, and industry. They also are active participants in the FDA Genetic Toxicology Network, the CDER Genetic Toxicology Network, and other interagency workgroups.

The Division's research is divided into three research areas: 1) genetic-toxicology research addresses the development of methods to assess the potential for chemicals to negatively impact human-genetic material or the function of the genetic material, 2) dietary research primarily focuses on the potential hazards of dietary supplements, and 3) omics research, coupled with more traditional approaches, is being used to improve the ability of FDA to incorporate new and powerful technologies into regulatory decision making.

DGRT activities provide both direct support for, and the generation of, new approaches used by FDA Centers and, in particular, provide research and expertise directly related to the FDA Critical Path Initiative.

FY 2008 Accomplishments

In FY 2008, DGRT scientists actively participated in providing genetic-toxicology advice to FDA Centers. These consultations included general advice concerning the conduct and interpretation of data from specific assays as well as evaluation of data from FDA submissions. DGRT scientists participated in the Genetic Toxicology Working Group of the ICCVAM (Interagency Coordination Committee on the Validation of Alternative Methods) and provided advice on new international guidelines for the conduct of the *in vitro* micronucleus assay. DGRT scientists were, and will continue to be, involved in

discussions concerning the appropriate follow-up strategies for chemicals (primarily pharmaceuticals) found to be positive in genetic-toxicology tests conducted as part of the drug-safety evaluation.

Specific DGRT research accomplishments include:

1. Completed a study in collaboration with researchers in NCTR's Division of Biochemical Toxicology and investigators in the Carcinogenesis Division, National Health and Environmental Effects Research Laboratory of the Environmental Protection Agency (EPA) that addresses the shape of the dose-response curve for low-dose exposure to carcinogens. NCTR research using this ACB-PCR (allele-specific competitive blocker-polymerase chain reaction) technology indicates that this approach provides the opportunity to detect the rare mutations involved in the etiology of cancer prior to the development of the actual visible tumor. This appears to be a promising biomarker that may provide a strategy that might ultimately lead to the replacement of the traditional two-year cancer bioassay and hasten the development, safety assessment, and approval of new drugs.
2. Completed a study in collaboration with the Hamner Institute to evaluate *p53* mutation in the nasal tissue of rodents exposed by inhalation to formaldehyde.
3. Continued two studies evaluating the presence of *p53* mutations in colon cancer from both mice and humans.
4. Continued studies to evaluate gene-expression changes in rodents exposed to comfrey (an herbal medicine) and riddelliine (an herbal tea in certain regions of the world), and aristolochic acid (a carcinogenic herbal compound). This research follows and expands earlier research with these compounds showing that all three can induce mutation following *in vivo* exposure.
5. Expanded research to understand the mechanistic basis of the *in vitro* regulatory assay—the mouse lymphoma assay (MLA).
6. Continued a comprehensive study to assess methylphenidate-induced genetic damage. This study, funded by the National Institute for Child Health and Development (NICHD), aims to characterize both behavioral changes in methylphenidate-exposed nonhuman primates and the metabolism of the drug in young rodents. Methylphenidate is a drug often prescribed to children to control Attention Deficit Hyperactivity Disorder (ADHD).
7. Continued the validation of a new approach for directly analyzing mutations. This assay uses fluorescent probes to detect mutation in the endogenous X-linked *PIG-A* gene. The detection of mutations in this gene does not require cell culture (as do many other *in vivo* mutation-detection methods) and lends itself to both *in situ* and high-throughput analyses in humans and animal models. These properties make *PIG-A* an attractive reporter-gene for *in vivo* mutation studies. This project received special funding as a Critical Path Project to develop this approach for use in humans.
8. Initiated a study in collaboration with CDC (Centers for Disease Control) to evaluate the relative mutagenic potential for a series of cigarette condensates.

9. Initiated a study to gain expertise in the comet assay and conduct research to evaluate the important parameter of this technique. The ultimate goal of this project is to provide information and expertise that can be used to assist with the development of guidance documents for the conduct of this assay.
10. Completed a project evaluating the relative sensitivity of neonatal animals and adult animals to mutagens. This project was directed at addressing the issue of young animals as a subpopulation sensitive to exposure to mutagens/carcinogens.

FY 2009 Plans

1. DGRT scientists will continue studies applying the new genotypic-selection technology measuring specific rare mutations in cancer-causing genes. This technology will be applied to understand the shape of the dose-response curve at low dose. A new emphasis will be placed on using this technology as a biomarker to identify potential carcinogens—thus providing an alternative to the two-year cancer bioassay. A new research effort will be directed toward understanding the background frequency of these cancer mutations in “normal” individuals. This will include the potential impact of rodent strain and age of the rodents. In addition, efforts will be made to make the technology more rapid and easy to conduct.
2. DGRT scientists will continue to investigate the possibility of using the new genotypic-selection technology to determine the number of specific tumor mutations still present following the treatment of tumors with cancer chemotherapeutics. Because this technology can detect these cancer biomarkers when they are present at a low frequency, it should be possible to use this approach to evaluate the efficacy of cancer treatment. The technology could readily determine whether a particular treatment is effective for a particular patient—thus providing a personalized-medicine approach to evaluating the efficacy of cancer therapy.
3. DGRT scientist will continue research to develop and characterize the *PIG-A* assay. Once developed and characterized, this assay will be applicable for use in human-clinical trials to assess the potential for mutagenic activity.
4. In collaboration with scientists in the Division of Biochemical Toxicology, the AIDS studies to model the use of antiretroviral-drug combinations to prevent the transmission of the virus from HIV-pregnant women to their children will continue. Human-clinical data suggest that a major target for the toxicity of AIDS-therapeutic agents is the mitochondria, and studies will be conducted to evaluate the long-term effects of perinatal treatments to mice on mitochondrial-DNA copy number and mutation.
5. In direct response to an FDA need, Division scientists will continue the program using the comet assay. This assay measures the ability of chemicals to induce DNA-strand breakage and is used internationally for hazard identification. The results of this project will identify appropriate parameters for conducting the assay and will be used to help develop the guidance for conducting the assay.

6. In direct response to an FDA need, a project will be initiated to evaluate various measures of cytotoxicity and other assay parameters for the *in vitro* micronucleus assay.
7. The collaboration with CDC evaluating the relative mutagenic potential for a series of cigarette smoke condensates will be completed.
8. As a part of the evaluation of three herbals, the new microRNA technology will be applied to see if it may be possible to identify markers associated with the development of tumors.
9. A new effort to evaluate the current genetic-toxicology regulatory-test battery for assessing the potential mutagenicity of nanomaterials will be started.
10. A new capability will be established to provide for the use of molecular-cytogenetic techniques in future research projects.

Contribution to FDA's Strategic Goals

The research conducted by the Division of Genetic and Reproductive Toxicology contributes primarily to FDA Strategic Goals 2 and 3.

FDA's Strategic Goal 2 (Improve Patient and Consumer Safety)

Genomic technologies are beginning to provide new tools for making better public-health decisions. International research efforts are providing the scientific and medical community with an increased understanding of the genetic material and how it functions in both humans and rodents. Utilizing this information, new molecular technologies are being rapidly developed and can be used to evaluate structural and functional changes to the genetic material of both rodents and humans. The Division is using new technologies, in combination with more traditional approaches, to address various research questions. While current technologies in the field of genetic toxicology generally evaluate single endpoints, the new genomic technologies are providing the opportunity to detect alterations in a number of endpoints. In the future, these new approaches to evaluate toxicity will allow for the integration of information across the various types of adverse health outcomes. For instance, when these technologies are fully developed, it will be possible to concurrently evaluate chemicals for their ability to cause cancer, to impact the nervous system, to cause birth defects, and to modify the immune function.

FDA's Strategic Goal 3 (Increase Access to New Medical and Food Products)

DGRT provides expert advice and innovative research to the other FDA Centers—thus contributing to FDA's mission of advancing public health. Several DGRT research projects involve the development of new and innovative technologies and approaches that support the regulatory Centers and, in particular, the FDA Critical Path Initiative. The Division received funding for a special Critical Path project to develop the *PIG-A* assay for use in humans.

Genetic toxicology is concerned with the ability of chemicals to alter genetic material. The FDA requires that petitioners provide data evaluating the potential genetic toxicity of their products as a part of the product-approval process. Because genetic damage is

believed to be important in tumor development, this information is used as a part of the evaluation of suspected carcinogens. Regulatory decisions are based not only on the identification of potentially genotoxic substances, but also on an understanding of their mode-of-action. Research within the Division focuses on the development and validation of new methods to assess genetic risk. Bacterial and tissue-culture approaches are commonly used to detect potential genotoxicity and to generate hypotheses concerning the basic mechanisms of genotoxicity. While the Division utilizes *in vitro* approaches, it specializes in the development and validation of *in vivo* mammalian systems and the incorporation of these methods into risk-assessment strategies. An increased understanding of mutational mechanisms, combined with test systems that have an increased ability to detect genetic damage, will provide FDA with better information for decision making. As new assays are validated, Division scientists will continue to work with international scientists to assure the harmonization of protocols and the development of guidelines to assess genetic hazards.

Division of Microbiology Summary of Activities

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Introduction

The Division of Microbiology serves a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology as well as respond to microbial surveillance and diagnostic needs for research projects. The Division of Microbiology research projects are based on FDA strategic goals and programmatic expertise. The research program is divided into five areas: 1) Food Safety, Food Biosecurity, and Methods Development; 2) Antimicrobial Resistance; 3) Gastrointestinal Microbiology and Host Interactions; 4) Environmental Biotechnology; and 5) Microbiological Surveillance and Diagnostic Support of Research.

FY 2008 Accomplishments

Food Safety, Food Biosecurity, and Methods Development

Division staff played a critical role in providing data important for ensuring the safety of foods. Specific research accomplishments are listed below.

1. Division investigators, in collaboration with the Center for Veterinary Medicine (CVM), Arkansas Public Health Laboratories, and the United States Department of Agriculture (USDA), are conducting genetic and epidemiological studies on the prevalence and spread of *Salmonella Javiana* in patients across Arkansas.
2. Eighty-one strains of *Aeromonas veronii*, an opportunistic pathogen, were isolated from farm-raised catfish. Polymerase chain reaction (PCR) protocols detected the presence of 8/10 virulent genes in more than 70% of isolates. The results indicated that farm-raised catfish is a source of pathogenic *A. veronii*.
3. Two hundred fifty *Salmonella enterica* strains were isolated and characterized from seafood samples provided by FDA Pacific Regional Laboratories. The samples were taken from seafood imported into the United States from 20 different countries. Fifty-five strains were resistant to at least one antibiotic tested, and five percent of the strains were resistant to more than one antibiotic. Pulsed-field gel electrophoresis (PFGE) of *Xba*I-digested DNA of multi-drug resistant strains showed all these strains were genetically distinct.
4. In continuation of the research funded by an Interagency Agreement (IAG) with the USDA and the Department of Homeland Security on the survivability of *Bacillus anthracis* in food, Division scientists have shown that egg white completely inactivates *B. anthracis* spores at 35°C. The inactivation of spores is believed to be due to the presence of lysozyme in egg white. Data from this study suggests that lysozyme could potentially be used as an additive to suppress

the growth of *B. anthracis* in ground beef and in developing counter measures and risk-assessment models on food biosecurity.

Antimicrobial Resistance

1. Researchers in the Division of Microbiology, in collaboration with CVM, University of North Dakota, and Marshfield Clinic Research Foundation, have shown that *Salmonella* Heidelberg, isolated from pre- and post-harvest turkey sources, were resistant to multiple drugs, and that high-molecular-weight plasmids may mitigate the transfer of drug resistance among *S. Heidelberg* with diverse-genetic profiles.
2. Division scientists, in collaboration with the USDA and the West Virginia University, have used the DNA-microarray technology for identifying genes that are responsible for mitigating drug resistance in *Salmonella*. This study demonstrated that *Salmonella* species, isolated from the preharvest poultry environment with no prior history of antibiotic usage, harbor genes that can render them resistant to several antimicrobials used in poultry and humans.
3. Division scientists have investigated the effect of exposure of bacteria from the human-gastrointestinal tract to fluoroquinolones and found that these drugs not only induce mutations, which result in increased fluoroquinolone resistance, but also may make some resistant strains more virulent. One fluoroquinolone-resistant strain of *Clostridium perfringens* produced more alpha and theta toxins, which mediate the onset of gas gangrene, than the wild-type strain.
4. Microbiology scientists have identified several novel proteins in *Staphylococcus aureus*, which may be important for virulence and, potentially, a new antimicrobial target. One protein in particular, hyaluronidase, will be assessed for its ability to cause disease. In addition, this protein may have potential as a novel means to differentiate *S. aureus* from other staphylococcal species.

Gastrointestinal Microbiology and Host Interactions

1. Division scientists have found that exposure of anaerobic bacteria from the human gastrointestinal tract to fluoroquinolones results in increased activities of multidrug transport proteins in some strains. After exposure to fluoroquinolones, the activity of one transporter increased, but there was a decrease in susceptibility to high concentrations of fluoroquinolones. Genetic analysis indicated similarity of this transporter to other drug transporters responsible for the resistance to other antimicrobial agents.
2. In a Cooperative Research and Development Agreement (CRADA) with Pfizer Animal Health, Division scientists studied degradation of the veterinary antimicrobial cephalosporin, ceftiofur, by bovine-intestinal microbiota. They isolated and characterized bacteria that had β -lactamase enzymes and found that *Bacillus* spp., *Roseomonas* spp., and *Azospirillum* sp. metabolized ceftiofur to compounds without bactericidal activity. They also found that *Bacillus* spp. and *Bacteroides* spp. use multiple serine-based and metallo-beta-lactamase enzymes for the primary enzymatic step in the degradation of ceftiofur,

minimizing the excretion of ceftiofur to the environment that may result in the resistance of potential pathogens.

3. A medium simulating vaginal secretions has now been modified to support the growth of several *Lactobacillus* sp. as well as several toxic-shock syndrome toxin-1 (TSST-1) producing strains of *S. aureus*. This medium has thus far been used to demonstrate the inhibitory affect of *Lactobacillus* sp. toward *S. aureus* in a co-culture system.
4. In an FDA Office of Women's Health (OWH) project, Division scientists found that vaginal-epithelial cells are directly involved in host inflammatory-response recruitment via activation of expression of pro-inflammatory cytokines. *C. albicans* infection causes apoptosis inhibition in these cells. Estrogen is antagonistic toward this pro-inflammatory response and also anti-apoptotic. Probiotic lactobacilli modulate expression of the inflammatory response genes and recover sensitivity to apoptosis induction. This study clarifies the interactions of probiotics, pathogens, and the human consumer for advancement of personalized medicine.
5. An OWH project is currently ongoing to perform assessment of the effects and metabolism of synthetic azo colorants used in women's cosmetics on human-skin microbiota. Division of Microbiology scientists have presented data examining the potential of the skin microbiota to metabolize azo dyes, performed a survey on metabolism of Sudan azo dyes found as contaminants in the food supply by predominant intestinal microorganisms, and provided evidence for significantly enhancing reduction of azo dyes in *Escherichia coli* by expressed azoreductase of *Enterococcus faecalis*.

Environmental Biotechnology

Division scientists have been assessing potential environmental impacts of some FDA-regulated chemicals, such as polycyclic aromatic hydrocarbons (PAHs) and antimicrobial agents. To this end, microbial processes have been used to elucidate the removal mechanism of these pollutants.

1. Microarray experiments were performed to determine the change of microbial community with respect to the environmental fate of PAH compounds. Soil samples contaminated with PAHs have undergone real-time PCR analysis, which revealed a positive relationship between the number of gene copies involved in the degradation of PAHs and the degree of PAH degradation in soils. Division scientists have studied the structural basis of ring-hydroxylating oxygenase with respect to substrate specificity of the enzyme.
2. Research on the degradation of antimicrobial fluoroquinolones to biologically inactive products is continuing in the Division. Bacteria were isolated from wastewater and selected for resistance to five fluoroquinolones. One *Escherichia coli* strain had a ciprofloxacin-acetylating gene and resistance mutations in the gyrase A and topoisomerase IV genes. High-performance liquid chromatography and mass spectrometry showed that it inactivated both ciprofloxacin and norfloxacin by N-acetylation.

Microbiological Surveillance and Diagnostic Support of Research

During FY 2008, program personnel worked to prevent the introduction of microbial pathogens into NCTR animal colonies by: 1) screening the primate colony for the presence of *Salmonella*, *Shigella*, and *Campylobacter* spp., 2) closely monitoring quarantined Lean Zucker rats for the presence of *Staphylococcus aureus*, 3) testing the animal quarantine area for the presence of *Pseudomonas aeruginosa*, and 4) working closely with the Division of Veterinary Services to monitor the success of a *Helicobacter*-eradication program in one of the mouse breeder colonies. Routine monitoring of the animals, environment, food, and water from the breeder colonies was a continuing priority.

FY 2009 Plans

Food Safety, Food Biosecurity, and Methods Development

1. Researchers will analyze patterns of antimicrobial-susceptibility profiles and investigate the genes harbored by *S. Javiana* that contribute to their pathogenicity in humans.
2. In collaboration with the NCTR's Division of Biochemical Toxicology, Arkansas Public Health Laboratory, CVM, and USDA, researchers in the Division of Microbiology will initiate studies to investigate the disease-causing potential of Enterohemorrhagic *E. coli* O157:H7 (EHEC) and its antigenic serogroups from human origin and foodborne outbreaks, and develop assays for rapidly detecting Shiga toxins in processed foods.
3. In collaboration with FDA Pacific Regional Laboratories, Division researchers will initiate projects to develop rapid and sensitive molecular methods to detect foodborne pathogens that include *Salmonella*, *E. coli* O157:H7, and *Shigella*.
4. The Division staff will continue working on a project in collaboration with USDA on the survivability of *Bacillus anthracis*. Division scientists will analyze the effect of egg white added to beef and milk on the survival of *B. anthracis* Sterne, *Salmonella*, *Staphylococcus*, *Enterococcus*, and *E. coli*.
5. A comprehensive study to understand the host-pathogen interactions using *Bacillus anthracis* Sterne as a pathogen and human intestinal, skin, and pulmonary-epithelial cell lines to elucidate the anthrax disease pathway(s) will be conducted.

Antimicrobial Resistance

1. In collaboration with CVM, Arkansas Regional Laboratories, and South Eastern Regional Laboratories, researchers in the Division of Microbiology will continue to investigate the prevalence of fluoroquinolone-resistant bacteria isolated from imported shrimp sold in retail stores. Research will be undertaken to elucidate the molecular mechanism of fluoroquinolone resistance in these organisms and to study the transferability of drug resistance to other commensals and clinical strains of bacteria.
2. Division scientists will use genetic analysis to continue evaluating the effect of antimicrobial agents on the physiological changes in *Clostridium perfringens* that

result either in increased virulence or the production of enzymes or byproducts whose activities affects human health.

3. Division scientists will initiate the process of obtaining BSL 3 (biosafety level 3) certification to examine the protective affect of avian-influenza hemagglutinin expressed from yeast in mice against highly pathogenic avian-influenza virus.
4. Division scientists will initiate studies to investigate the pathogenic role of staphylococcal hyaluronidase.

Gastrointestinal Microbiology and Host Interactions

1. Division scientists will continue to conduct the OWH-funded project to perform assessment of effects and metabolism of synthetic azo colorants used in women's cosmetics on human-skin microbiota.
2. Division scientists, in collaboration with CVM, will evaluate the effect of antimicrobial agents on bacteria from the human-intestinal tract and analyze the bioavailability of these compounds as the result of human exposure to antimicrobial agents.
3. Division scientists will continue to study the gene-expression responses of vaginal-epithelial cells to *Candida albicans* and probiotic lactobacilli.
4. Division immunologists will continue to explore the mechanism of probiotic bacteria in *Salmonella* infections of mice.
5. Division scientists will continue to evaluate the molecular basis for the increase in antimicrobial resistance in the *Clostridium* strains from the gastrointestinal tract that appear to have identical mutations in the target genes.
6. Division scientists will continue to develop an *in vitro* model simulating the vaginal tract for the purpose of examining the interaction between naturally occurring lactobacilli and lactobacilli engineered to express the staphylococcal cell wall degrading enzyme, lysostaphin.
7. Division scientists will study the effect on intestinal-microbiota population on an investigational botanical drug Silymarin.

Environmental Biotechnology

1. Division scientists will determine the fate of polycyclic aromatic hydrocarbon (PAHs) and PAH catabolic genes in a variety of soil systems using high-throughput PCR-based experiments.
2. Division scientists will screen samples from wastewater-treatment plants for bacteria and fungi that degrade or transform fluoroquinolones.

Microbiological Surveillance and Diagnostic Support of Research

In FY 2009, the Microbiological Surveillance and Diagnostic Support group will continue working to ensure that the research-animal population remains healthy and disease-free.

Contribution to FDA's Strategic Goals

The Division of Microbiology staff is conducting a number of projects in conjunction with other FDA Centers to provide critical research that primarily supports FDA's Strategic Goals 2 and 4.

FDA Strategic Goal 2 (Improve Patient and Consumer Safety)

Recent outbreaks of *Salmonella* in peanut butter and *E. coli* O157:H7 in spinach and tomatoes underscores the urgent necessity to address the threat of these foodborne pathogens in our food supply. Food safety and biodefense are important considerations to FDA and the national security of the United States. A major emphasis of the research in the Food Safety, Food Biosecurity, and Methods Development area of the Division of Microbiology is to conduct scientific research that will supplement the regulatory decisions of FDA to ensure the safety of our food supply in the "farm-to-the-fork" continuum. The studies conducted in this research area highlight the use of molecular methodologies to source-track the origin and dissemination of pathogenic and drug-resistance bacteria from different food animal, veterinary, or clinical origin. The ability of this high-density microarray-biochip technology to rapidly detect hundreds of antimicrobial-resistance genes can be useful to FDA and other state and federal agencies in analyzing patterns of drug resistance in foodborne pathogens. The fluoroquinolone-resistance data in foodborne pathogens will aid the agency to regulate the importation of aquaculture products from countries that abuse fluoroquinolones in shrimp cultivation.

FDA Strategic Goal 4 (Improve the Quality and Safety of Manufactured Products and the Supply Chain)

The Division of Microbiology research staff has expertise and long-standing interest in assessing risks to the gastrointestinal microflora of humans when antimicrobials are ingested through foods, probiotics, and dietary supplements. Division scientists provide guidance and expert advice to FDA, other national regulatory agencies, and the World Health Organization on the potential human-health risks associated with the use of antimicrobial agents, competitive-exclusion products, probiotics, and dietary supplements in veterinary and human clinical medicine.

The research conducted in the Division of Microbiology will allow FDA to gain a clearer understanding of how food contaminants, drugs, probiotic products, dietary supplements, and xenobiotic substances affect the intestinal microbiota and how changes in this population may affect human health. Evaluations of how probiotic bacteria affect epithelial-cell responses to pathogens in the intestinal and vaginal tracts will help regulators assess and monitor probiotic products that are increasingly common in the marketplace.

Environmental biotechnology research in the Division of Microbiology on the environmental fate of FDA-regulated drugs is highly relevant to the prevention of microbial antibiotic resistance. Before a veterinary drug can be marketed, FDA requires an environmental risk assessment. If the drug residues can be metabolized to inactive products, they will no longer select for bacterial resistance. This research is increasing our understanding of the metabolism of antibiotics and their effects on the environment.

Division of Neurotoxicology Summary of Activities

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Introduction

Fifty-million Americans have a permanent, neurological disability that limits their daily activities. One in three will experience some form of mental disorder during their lifetime. Annual health care, lost productivity, and other economic costs associated with brain-related diseases are estimated to exceed \$500 billion. Disability from depression alone exceeds that of diabetes, hypertension, gastrointestinal, and lung diseases and costs over \$43 billion annually. The number of persons with Alzheimer's and other age-related neurological disorders will increase dramatically as our population ages. Known and suspected causes of brain-related disorders include exposures to chemicals, such as therapeutic drugs, food additives, food products, cosmetic ingredients, pesticides, and naturally occurring substances. Recent advances in technology are currently providing our scientists with a variety of new tools with which to better study and understand the etiology of brain-related disorders and the mechanisms associated with chemically induced neurotoxicity and to further reduce the risks associated with neurotoxic events.

The number of neuroactive chemicals that require FDA regulation is estimated to be in the thousands. Thus, identifying methods and approaches for assessing neurotoxicity is critical for the development of guidelines applicable for the assessment of neurotoxic risk. It is clear that chemicals that are known or suspected causes of brain-related disorders are vital to the national economy and our quality of life. Therefore, the challenge is to determine at what doses, or exposure levels, and under what conditions these compounds can be used effectively while minimizing the likelihood that they will cause adverse effects on the nervous system.

The overall goals of the Division of Neurotoxicology are to develop and validate quantitative biomarkers and identify biological pathways associated with the expression of neurotoxicity. Towards this end, specific research efforts address several focal areas of fundamental research designed to broadly examine the involvement of: 1) monoamine-neurotransmitter systems as targets for neurotoxicity, 2) mitochondrial dysfunction and oxidative stress as mechanisms of neurotoxicity, 3) the NMDA (N-methyl-D-aspartic acid) receptor complex as a mediator of adult and developmental neurotoxicity, and 4) the role of amyloid β -peptide (A β) aggregation in the expression of neurotoxicity. An increased understanding of the processes associated with neurotoxic outcomes will provide opportunities for improved assessments of risk and identification of potential therapeutic approaches. The strategy employed for achieving these goals has been to use multidisciplinary approaches that capitalize on the neurochemistry, molecular neurobiology, neuropathology, neurophysiology, and behavioral expertise of

Division personnel. The Division is expanding capabilities in the area of imaging by adding both microPET and magnetic resonance imaging (MRI) instruments and personnel. In addition, efforts to develop sensitive, high-throughput systems for screening potential neurotoxicants are underway. Other unique features of the Division's research capabilities include the ability to: 1) determine chemical concentrations and cellular-level interactions in target tissue, 2) determine changes in gene and protein expression associated with chemical exposures, 3) effect high-throughput, comprehensive cognitive or behavioral assessments, 4) employ multiple species including nonhuman primates, rodents, and, in some cases, humans, in the risk-assessment process to reduce the uncertainty associated with extrapolating findings across species, and 5) develop novel histochemical tracers to aid in the evaluation of chemical-induced pathologies.

FY 2008 Accomplishments

Research protocols were implemented or continued to provide data important for the regulatory needs of the agency with respect to acrylamide (a ubiquitous food contaminant), pediatric anesthetic agents (including ketamine), the central nervous system stimulants amphetamine and methylphenidate (widely used in the treatment of Attention Deficit Hyperactivity Disorder), and nanoparticles.

Under a Cooperative Research and Development Agreement (CRADA), an assessment of the effects of the chronic administration of pramipexole, a dopamine D3-receptor agonist, was completed in a juvenile nonhuman primate model. This compound is used for the treatment of Parkinson's disease and Restless Leg Syndrome (RLS) in adults and is being considered for pediatric use in the treatment of Tourette's and RLS. This study provided invaluable information concerning expected outcomes of chemicals known to interact with specific subcellular targets during development.

In partnership with colleagues at CDER and NICHD (National Institute of Child Health and Human Development), Division staff demonstrated that ketamine-induced neural-cell death in our perinatal monkey cell-culture model is both apoptotic and necrotic in nature. Based on periods of rapid synaptogenesis, the timing of exposures becomes critical when comparing rodent, nonhuman primate, and human-neurotoxic outcomes. *In vivo* nonhuman primate studies have helped to identify developmental periods during which sensitivity to ketamine is greatest and also to explore aspects of exposure duration that contribute to toxicity. Importantly, the use of nonhuman primate and rodent models are beginning to help identify compounds that may be able to prevent or ameliorate anesthetic-induced neurotoxicity. Studies in rats and mice were conducted to understand the neuroprotective mechanisms of L-carnitine. Regulatory briefings have helped to determine relevant-data needs and possible labeling changes based on new data generated in the Division. In addition, Division scientists were consulted by CDER reviewers to assist with issues concerning the potential neurotoxicity of anti-epileptic drugs when used in the pediatric setting.

Work was initiated to evaluate damage to brain vasculature and meninges after exposure to amphetamines by evaluating changes in vascular-related genes at the

transcriptional and translational levels. Data thus far indicate that the meninges and surface vasculature of the brain are susceptible to damage when pronounced hyperthermia accompanies amphetamine exposure. Other observations suggest that the amphetamines produce pathological changes in blood-brain barrier (BBB) permeability, and the neurotoxic effects of methamphetamine, kainic acid, and acrylamide were described using a new, novel histochemical tracer, Black-Gold II.

Studies on the assessment of human brain/cognitive function using the NCTR Operant Test Battery—the same instrument used in the Division’s Nonhuman Primate Research Center—continued, primarily in children with depression or anxiety disorder and in children exposed to opiates during the perinatal period. These studies are exemplary of translational neuroscience and highlight the cross-species comparison capabilities within the Division.

In support of many of our areas of research, genomic, proteomic, and bioinformatics approaches were developed or enhanced to allow for the identification of gene- and protein-expression profiles associated with neurotoxic events. These included studies on chemically induced mitochondrial dysfunction, where significant increases in the gene expression of a specific uncoupling protein were demonstrated. Identification of such specific events can serve to elucidate mechanisms and provide markers of toxicity. A microPET imaging device began providing the opportunity to follow such events noninvasively in longitudinal fashion and will eventually provide time-course information on lesion development, severity, and recovery.

In collaboration with colleagues at CDER, CDRH, and Wright Patterson Air Force Base (WPAFB), Division staff demonstrated that metal oxide-based nanoparticles (manganese, silver, copper, and aluminum) produce free radicals and induce oxidative stress in both cell-culture and animal models, effects that are associated with selective alteration in the expression of genes associated with apoptosis and oxidative stress. These preliminary data are providing mechanistic information that will help researchers understand the potential risk of nanoparticles to human health.

Studies on C-75, a compound that inhibits the action of carnitine (required for the transport of fatty acids from the cytosol into mitochondria during fat catabolism) in the central nervous system and induces anorexia, demonstrated that both dopamine and free-fatty acids participate in the cellular control of energy balance.

FY 2009 Plans

Much of the work for the coming year will involve continuation of the efforts mentioned above and focus on specific agency regulatory needs. These include continuing the analyses and interpretation of data from our studies on acrylamide, pediatric anesthetics, nanoparticles, and amphetamines and related compounds. A comprehensive protocol focusing on the developmental toxicity of the ubiquitous plasticizer, Bisphenol A, and a protocol to assess the efficacy and toxicity of a variety of potential therapeutic agents in a transgenic-mouse model of Alzheimer’s disease will be developed. Building renovations will expand the capacity of the Nonhuman Primate

Research Center and provide a suite for a new MRI system and the Division's existing microPET. Combining the power of MRI with microPET will dramatically increase imaging capabilities and enhance our efforts to describe and define neurotoxic events as they occur over time in living-animal models.

In continued fundamental research into the consequences of mitochondrial dysfunction and oxidative stress, investigations will focus on posttranscriptional and translational regulation occurring during early responses to metabolic stress. cDNA arrays, RT-PCR (reverse transcriptase-polymerase chain reaction), and metabolomic profiles obtained using NMR (nuclear magnetic resonance) technology will be used in attempts to identify biologically significant changes in gene expression that accompany mitochondrial dysfunction. Such analyses will place emphasis on the involvement of apoptotic and inflammatory responses in these processes. To further define the neurotoxicity associated with the food contaminant 3-NPA, a mitochondrial inhibitor, and the ability of L-carnitine to protect against this toxicity, studies will be conducted on the integrity of the peripheral nervous system by assessing nerve conduction velocities.

To assist the agency with the rapid determination of the neurotoxicity of a vast array of regulated chemicals and food contaminants, the Division will begin development of a high-throughput, *in vitro* (zebrafish) system. This approach to identifying potential vertebrate toxicants will have broad applicability and be relevant for a variety of life stages, from fertilization throughout development.

Further utilization of omics techniques should allow for the identification of specific genes and pathways involved in the expression of neurotoxicity and incorporation of state-of-the-art imaging capabilities—microPET and MRI—will provide a new dimension to our abilities to understand adverse neural events. In addition to these specific efforts, Division scientists will continue to address several main areas of fundamental research designed to broadly examine the involvement of: 1) monoamine neurotransmitter systems in the development of neurotoxicity and associated vascular damage; 2) mitochondrial dysfunction and oxidative stress as mechanisms of neurotoxicity; 3) the NMDA-receptor complex as a mediator of adult and developmental neurotoxicity; and 4) the role of A β in neurodegenerative processes. New projects will be implemented to develop novel histochemical tracers for the localization of various elements of the brain vasculature and to use these tracers to illuminate the effects of neurotoxicants.

In collaboration with colleagues at CDER, CDRH, and WPAFB, Division staff plan to study the effects of nanoparticles and carbon nanotubes on the integrity of the BBB. A microvascular endothelial-cell culture will be established to model the BBB and allow the study of its permeability to nanoparticles. The toxicity of selected nanoparticles will be studied in both *in vitro* and *in vivo* models.

Contribution to FDA's Strategic Goals

Research in the Division of Neurotoxicology contributes primarily to FDA Strategic Goals 2 and 3.

FDA Strategic Goal 2 (Improve Patient and Consumer Safety)

Substantial effort is being made to specifically address issues of regulatory concern related to acrylamide (a food contaminant), anesthetic agents (particularly those used in the pediatric setting), and stimulant medications. Research to elucidate the mechanisms surrounding the potential neurotoxicity associated with the pediatric use of anesthetic agents, define sensitive periods of development, explore critical dose-response relationships, and develop protective therapeutic strategies will provide clinicians with the knowledge needed to minimize risk and protect public health. Research to determine the risks associated with amphetamine and related compounds—including hemorrhage, hyperthermia, and seizures—will help further clarify the conditions under which these products can be used safely. The development of high-throughput systems for the rapid detection of potentially neurotoxic compounds will help direct subsequent resource utilization in further defining the risks associated with their use.

FDA Strategic Goal 3 (Increase Access to New Medical and Food Products)

Division scientists continue to develop new approaches for the assessment of toxicity. Towards that end, the establishment of state-of-the-art imaging capabilities is providing opportunities to monitor the onset of toxic responses and to delve further into their mechanisms and time course. These imaging resources will provide the agency with the capabilities to get maximal information from invaluable animal models while minimizing the number of animals needed. Not only do these and similar efforts serve to strengthen FDA's base of operations, they also strengthen the scientific foundation of FDA's regulatory mission and the science that supports product safety. Many of these efforts involve partnerships within the agency, with industry, and with academic centers. In addition, Division staff continue to provide training for undergraduate and graduate students, postdoctoral fellows, visiting scientists, and FDA Fellows—many of whom will go on to serve the agency as employees endowed with the knowledge and expertise needed to preserve its science base.

By developing effective methods for elucidating the biochemical pathways that underlie the expression of toxicity, it should be possible to use those methods to assess the toxic or protective effects of new medical and nutritive products. Utilization of *in vitro* brain-cell preparations in our studies on the toxicity of anesthetic compounds is proving to be a valuable tool for understanding toxic mechanisms and should provide insight into possible rescue or protective approaches. Utilization of a transgenic-mouse model of Alzheimer's plaque deposition will be used to help delineate toxic mechanisms and illuminate potentially beneficial therapeutic strategies. Mechanistically based approaches are being applied to define and understand the potential of a broad range of drugs and other chemicals to produce neurotoxic effects during all stages of development and senescence. This kind of information will be invaluable in the development of new products.

Division of Personalized Nutrition and Medicine Summary of Activities

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Introduction

The Division of Personalized Nutrition and Medicine (DPNM) is charged with developing strategies, methods, and resources for improving individual and public health. The need for this Division and research paradigm resulted from data generated by the human genome and HapMap projects. These international efforts laid the foundation for one of the most significant scientific contributions to humankind—an evidence-based understanding that while humans are genetically similar, each retains a unique genetic identity that contributes to the wide array of biochemical, physiological, and morphological phenotypes in human populations. Parallel molecular genetic studies have demonstrated that nutrient and environmental chemicals directly or indirectly regulate the expression of one's genetic makeup.

While the research strategies of the 20th century yielded data and knowledge that extended our average lifespan and improved personal and public health, much of that knowledge was based on the average response of a population to a food, nutrient, or environmental chemical, or the average risk for carrying a specific allele of a gene involved in disease. Such knowledge may or may not be applicable to an individual with different genotypes or environmental exposures.

The overall goals of the DPNM are to develop and implement research strategies that account for genetic, environmental, and cultural diversity that influence expression of genetic makeups and produce knowledge for improving personal and public health.

These overarching goals will be met with three parallel efforts that develop:

- Integration of omics methodologies to assess an individual's health status and, as importantly, susceptibility to specific chronic conditions influenced by environmental factors including diet
- Means to capture and assess an individual's nutritional, environmental, and activity exposures
- Classification algorithms that integrate the data from omics and environmental assessments that will result in evidence-based and validated biomedical decision making

The Division has two branches—Biometry and Biology. The main function of the Biometry branch is to develop biometrical methods for all aspects of the FDA's mission, goals, and objectives. A subgroup within the Division analyzes all data from the National Toxicology Program (NTP). The Biology branch is focusing on the broad areas of pharmacogenomics and nutrigenomics—how individuals respond to drugs and nutrients in foods.

FY 2008 Accomplishments

The first permanent director arrived at the Division of Personalized Nutrition and Medicine in November 2007, following the reorganization of the Biometry and Risk Assessment Division and the Molecular Epidemiology Division in October 2006. The Director's background is in the emerging discipline of nutrigenomics, a foundational concept for personalizing nutrition and medicine. As the new leadership in the Division began formulating the Division's research plans, members of the two branches met major milestones in FY 2008.

The NTP subgroup of the Biometry branch completed 27 statistical reports for NTP protocols. This staff also provided statistical support, including protocol review for a number of additional NTP and non-NTP studies, reviewed protocols for the Institutional Animal Care and Use Committee (IACUC), and maintained correspondence with the FDA Statistical Association in Washington.

The statisticians in the Biometry branch contributed to four research projects and maintained communications with the scientists on risk-assessment methodology in the Interagency Risk Assessment Consortium. The research efforts focused on analyzing microarray data, developing classification algorithms to facilitate the use of high-dimensional genomic biomarkers, contributing to the development of statistical methods to analyze individual genes and biological pathways, and investigating hierarchical-probabilistic models for characterization of uncertainty in risk/safety assessment.

The Biology branch contributed to the development of a biomedical-focused, community-based participatory research program (CBPR) in collaboration with the U.S. Department of Agriculture (USDA) Agricultural Research Service (ARS) Delta Obesity Prevention Research Unit in Little Rock, Arkansas, and the Boys, Girls, and Adults Community Development Center (BGACDC) in Marvell, Arkansas. CBPR may bridge population-based research strategies to the individual. The study is analyzing the levels of selected vitamins and metabolites in the serum of children attending a five-week summer day camp at the BGACDC. The concept of merging biomedical research to CBPR methods for personalizing nutrition recommendations was published in peer-reviewed journals. The Division is also developing a genomic core laboratory focused on whole-chromosome analyses and resequencing of candidate genes involved in polygenic phenotypes. The Division Director also participated in, and was first author of, a meeting report of the Human Variome Project (HVP)—(<http://www.humanvariomeproject.org/>), which was published in the journal *Human Mutation*. The HVP is organizing an international effort to resequence genes involved in human diseases.

FY 2009 Plans

The DPNM is extending its CBPR program to include the association of an individual's response to improved nutrient intakes with their genetic makeup and candidate genes involved in obesity and Type 2 diabetes. The CBPR program collaboration with the BGACDC and the USDA-ARS is being expanded to include the Washington and Lee

University Shepard Poverty Program, which is providing two summer interns to assist with the efforts in the Delta region.

DPNM initiated a program in stem-cell research with the recruitment of a scientist and a support-staff specialist from the University of Arkansas for Medical Sciences. They will be joining members of the Division with expertise in embryology, teratology, and molecular-genetic analyses of cells in culture. This new program is being vertically integrated into new programs in mouse-epigenetics (the changes in RNA expression information without a change in DNA sequence) studies being developed in the Division in collaboration with scientists in the Division of Biochemical Toxicology. Integrating data and results from the model systems of stem cells, laboratory animals, and humans will provide results ranging from mechanisms to applications in humans.

DPNM is also developing a research protocol based on the concept of analyzing and understanding the “healthy state.” Health is often considered the absence of disease, and disease biomarkers may not be useful in predicting susceptibility to chronic diseases. The NCTR Healthy Challenge Study is a collaboration with other NCTR scientists in the Divisions of Systems Toxicology, Biochemical Toxicology, Neurotoxicology, Microbiology, and Genetic and Reproductive Toxicology who are experts in transcriptomic, proteomic, and metabolomic concepts and instrumentation. Scientists from academic institutions and companies are contributing expertise to studies of responses to the over-the-counter medication acetaminophen, exercise, and the oral-glucose challenge. An individual’s response to these challenges may be unique to their genetic makeup and provide information for long-term health outcomes.

Assessing nutrient intake (calories in) and physical activity levels (calories out) has been a challenge for the fields of nutrition, nutrigenomics, and personalized nutrition and medicine. DPNM met with members of the USDA-ARS Human Nutrition Center in Beltsville, Maryland, the National Institutes of Health (NIH), CFSAN, academic researchers, and company representatives to discuss the state-of-the-art in assessment tools, databases, and needs at a workshop in Spring 2009. The results of the workshop will be published and will describe current nutrient intake and physical activity assessment tools along with plans to develop comprehensive food-survey websites and databases, along with activity-monitoring software. These tools are much needed not only for research purposes, but when developed further, will have applications in clinics and community-wellness programs.

The Biometry branch will focus on the development of: 1) decision models for clinical assignments of patients based on the patient’s genomic features and disease phenotypes, 2) methods to identify genomic, proteomic, and metabolomic liver-toxicity biomarkers, and 3) computational algorithms that will efficiently compute adjusted p-values for the large numbers of subsets defined through gene ontology. In addition, the staff will investigate methods for integrating the associations between the genomic-predictor variables and phenotype-class variables (such as tumor types or treatment efficacy), predictive models, and computational methods for quantitative assessment of benefit/risk models for regulatory decisions in personalized medicine, and initiate

research on biostatistical approach for relative-risk ranking for food protection. The NTP staff will continue its critical mission of analyzing data from NTP studies.

DPNM's Biometry branch is the lead in developing a protocol for developing an integrated genomics knowledge base for rapid-threat assessment of enteric-foodborne pathogens. This project is in collaboration with the Divisions of Microbiology and Systems Toxicology.

Contribution to FDA's Strategic Goals

Research in the Division of Personalized Nutrition and Medicine contributes primarily to FDA Strategic Goal 2.

FDA Strategic Goal 2 (Improve Patient and Consumer Safety)

Research in the Biology branch contributes primarily to improve patient and consumer safety by increasing access to new medical and food products and by developing methods and knowledge for understanding differences based on individual genetic makeup. While the methods and knowledge are just beginning to be developed, the consumer and public are already exposed to genetic testing and products designed for individuals, even though the science to support those products is somewhat lacking.

The Biometry branch of the Division collaborates with scientists at NCTR and other FDA Centers by analyzing data with novel risk-assessment algorithms. Specifically, the Biometry branch estimates risks associated with toxic substances and helps set safe-exposure levels that correctly reflect underlying uncertainties. FDA relies on DPNM to: 1) conduct risk assessments for the regulation of specific products and in investigating generic risk-assessment issues, 2) develop mathematical models and computer systems for analyzing pharmacokinetic and pharmacodynamic components of toxic mechanisms, 3) develop classification algorithms for biomedical decision making, including identifying food hazards and assigning patients to drug therapies, 4) develop statistical methods for analyzing genomic, proteomic, metabolomic, and toxicoinformatic data, 5) apply statistical methods to evaluate toxicological, pharmacological, and nutritional concerns, and 6) provide expertise to NCTR scientists on the design, conduct, and analyses of research studies to evaluate the toxicity of regulated products. The Biometry branch is also contributing to the FDA's responsibilities to protect the food system in the United States.

Division of Systems Toxicology Summary of Activities

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Introduction

The Division of Systems Toxicology supports the development of new technologies and works to facilitate integration of data from multiple technology platforms for scientific application to questions that are in direct support of the FDA mission. Six Centers of Excellence comprise the Division of Systems Toxicology: Functional Genomics, Hepatotoxicity, Innovative Technologies, Metabolomics, Proteomics, and Toxicoinformatics. The goals of this Division include: 1) to provide technical expertise and guidance for the inclusion of omics and *in silico* data into the review process and within the drug-development process, 2) to identify new, more predictive biomarkers of toxicity, prognosis, diagnosis, and disease that will aid in the development and approval of safer and more effective medicines, foods, and medical devices, 3) to identify new approaches to improve food safety, cancer treatment, and medical imaging for less invasive diagnoses. When appropriate, biomarkers will be submitted for official qualification and new approaches patented if significant outside investment for their development is required.

The Center for Functional Genomics uses high-information content microarrays in the development of mechanistic and biomarker data for improved safety assessments. Whole-genome commercial arrays, as well as in-house fabricated custom microarrays, show great promise in drug-safety evaluation, and FDA is actively encouraging this new technology. Major efforts include the development of preclinical predictive toxicology biomarkers and continuing to serve as an FDA resource for genomics issues.

The Center for Hepatotoxicology addresses critical liver-injury issues by applying a systems-toxicology approach. The goal is to improve the identification of hepatotoxic compounds prior to human exposure and to augment the detection of early signs of injury in humans induced by drugs, chemicals, and disease processes. Biomarkers will be identified using integrated genomics, metabolomics, proteomics, and bioinformatics approaches.

The Center for Innovative Technologies uses multi-faceted approaches to address important issues of human health. Examples include a program in mass spectrometry-based analyses in counterterrorism, the use of flow cytometry for rapid detection of bacteria in food, and significant efforts in sensors and nanotube technology. In addition, the group provides computational approaches to predictive toxicology and efficacy.

The Center for Metabolomics aids in the assessment of preclinical and clinical safety issues as part of an FDA-wide biomarkers-development effort. This Center has initiated

active collaborations within NCTR, across FDA, and with academic and pharmaceutical-research groups to identify biomarkers of toxicity and disease.

The Center for Proteomics continues to develop and evaluate novel proteomic technologies with the aim of facilitating the translation of basic science to medical products, and facilitating proteomic research through collaboration with investigators to address FDA critical issues related to drug safety and efficacy.

The Center for Toxicoinformatics conducts research in bioinformatics and chemoinformatics and develops and coordinates informatics capabilities within NCTR, across FDA Centers, and in the larger toxicology community. A goal of the toxicoinformatics group is to develop methods for the analysis and integration of omics (genomics, proteomics, and metabolomics) datasets with classical in-life parameters. This group is taking an active role in supporting FDA's bioinformatics modernization plan, including the e-submission process.

FY 2008 Accomplishments

During FY 2008, Division scientists engaged in research addressing a variety of agency issues with special emphasis on Critical Path, food safety, and bioinformatics.

Accomplishments include the following:

- Identified potential metabolomic biomarkers of hepatotoxicity in a preclinical-test species
- Started and extended collaborations to examine urinary biomarkers of renal and hepatic injury in children
- Conducted mechanistic studies of hepatic effects of antidiabetic drugs, dietary supplements, and nongenotoxic and genotoxic rodent carcinogens
- Identified preexisting mitochondrial oxidative stress as a potential factor leading to idiosyncratic hepatotoxicity
- Completed Phase I of the liver-toxicity biomarker study to examine the multi-omic response in rats to tolcapone and entacapone
- Determined changes in gene-expression profiles of drug-metabolizing genes and other genes caused by hepatotoxins to address important issues in personalized medicine
- Investigated adverse effects to zidovudine (AZT), an anti-HIV drug
- Continued the development of ArrayTrack™ to warehouse, visualize, analyze, and interpret data from diverse omics technology as well as clinical and nonclinical data
- Supported FDA Bioinformatics Initiatives for Regulatory Use
- Continued participation in the review of the pharmacogenomics data submitted through the Voluntary eXploratory Data Submission (VXDS) program
- Started the Liver Toxicity Knowledge Base (LTKB) project to develop a resource for investigation hepatotoxicity
- Continued Phase II of the MicroArray Quality Control (MAQC) project to help define best practices for developing predictive signatures based on omics profiles

- Improved novel computational models that predict toxicity and efficacy of new drugs
- Conducted proof-of-principal experiments for a nanotechnology-based, targeted cancer therapy
- Further developed rapid technologies for detection of pathogens in food
- Established a new Center for Proteomics team who developed approaches for protein identification and quantitation using one-dimensional and two-dimensional liquid chromatography and Tandem mass-spectrometry (MS/MS)
- Conducted proteomic analysis of mouse-lymph nodes titanium dioxide (TiO₂) particles and identified protein signatures to specific TiO₂ nanoparticles
- Enhanced proteomic research capabilities by implementing high-resolution mass spectrometry and multiple mass spectrometric data-processing engines for FDA research needs
- Participated in National Center Institute/FDA interagency oncology task force for identifying analytical biomarker validation needs for targeted proteomics technologies

FY 2009 Plans

In FY 2009, the Division of Systems Toxicology will continue to emphasize the systems-biology approach for development of predictive biomarkers and mechanistic information for safety assessments of medical products and foods. Additional studies will focus on the development of improved *in silico* modeling approaches for drug safety and medical imaging and design of a new chemotherapeutic approach. To accomplish its mission, the Division of Systems Toxicology will:

- Continue development of an integrated, state-of-the-art omics platform consisting of microarray, NMR (nuclear magnetic resonance)- and MS-based metabolomic, lipidomic, and proteomic signatures to address issues of interest to FDA
- Provide technical expertise to FDA in genomic, proteomic, and metabolomic interpretation and guidance
- Continue to study the body's response to toxicants and disease processes using integrated omics analyses and conventional in-life assessments to identify new translational biomarkers of injury to improve detection and amelioration of drug-induced injury and disease progression
- Continue to develop computational models of biological activity, toxicity, and biomarker-pattern identification
- Continue development of the Liver Toxicity Knowledge Base
- Complete Phase II of the MAQC and MAQC-III to examine next-generation sequencing approaches
- Continue participation in FDA's bioinformatics modernization plan and take the lead in a pilot study for an agency-wide e-submission and review platform for all FDA-regulated products
- Continue to develop nanotechnology and sensor-technology efforts
- Develop technologies for proteome-wide identification of protein modifications

- Continue development of Food Quality Indicators as useful indicators of food spoilage
- Continue development of RAPID-B (Rapid Identification of Bacterial Pathogens) for the detection of pathogenic food contaminants

Contribution to FDA's Strategic Goals

Research in the Division of Systems Toxicology contributes to FDA Strategic Goals 2, 3, and 4.

FDA Strategic Goal 1 (Strengthen FDA for Today and Tomorrow)

The MAQC-III consortium aims to determine and identify the issues and challenges associated with the next generation of sequencing technology. It anticipates that the review of such data as a part of an Investigational New Drug (IND) and New Drug Application (NDA) submission will soon become FDA's major responsibility.

FDA Strategic Goal 2 (Improve Patient and Consumer Safety)

The entire Division is involved with developing potential preclinical and translational safety and disease biomarkers based on new metabolomic, genomic, and proteomic technologies. The unique aspect of this work is the integration of the various datasets coupled with computational biology to get a holistic systems view of the safety problems caused by medical products and of disease processes. This Division is building a Liver Toxicity Knowledge Base to improve reviewer's understanding of safety issues. In addition, new mass-spectrometric and flow-cytometric methods are being developed and validated for the detection of bacteria in food products. There is a continuing effort to develop sophisticated pattern recognition-based algorithms that use advanced noninvasive imaging scans to improve tumor diagnosis, which has the potential to enable early noninvasive screening.

FDA Strategic Goal 3 (Increase Access to New Medical and Food Products)

The Division is developing various bioinformatics tools to support FDA Voluntary Genomics Data Submission program, including ArrayTrack™, SNPTrack, and VISIONS. These tools allow the reviewers to easily access the information from both private and public domain—thus enhancing the FDA-review process. Novel computational models are being developed that predict drug safety and efficacy and such new methods will increase the number of safe and effective medical products.

FDA Strategic Goal 4 (Improve the Quality and Safety of Manufactured Products and the Supply Chain)

Scientists in the Division are working on methods to detect food spoilage in a commercial setting. This technology is now being commercialized and promises to provide consumers with on-the-spot information on the freshness of the food supply.

Division of Veterinary Services Summary of Activities

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Introduction

The Division of Veterinary Services (DVS) provides professional and technical support for all animal-related research projects at NCTR. The Division administers the Center's Animal Care and Use Program, which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). Included within the Division are contracted services for animal husbandry, veterinary care, diet preparation, and pathology. This workforce is stable, highly trained and skilled, and boasts a high percentage of certified employees in their respective disciplines.

The Division Director is a member of NCTR's Institutional Animal Care and Use Committee (IACUC), serving as Vice-Chair and Attending Veterinarian. The liaison between DVS and the IACUC ensures maximum efficiency in protocol planning and review, provision of the highest quality of animal care and use, and delivery of superior services to the NCTR research community.

DVS oversees the operation of five animal facilities consisting of over 112,000 square feet of space dedicated to providing state-of-the-art housing and care of research animals. A variety of housing options are available for rodent models including ventilated rack systems and automatic watering systems. A rodent-breeding operation established over thirty years ago provides many of the strains used for on-site experiments. A highly trained and American Association for Laboratory Animal Science (AALAS)-certified animal care staff provides a wide variety of husbandry and technical services in support of NCTR's AAALAC-accredited Animal Care and Use Program.

Provision of veterinary services of the highest quality to NCTR's research animals is a Division priority. Three veterinarians, two of whom are certified by the American College of Laboratory Animal Medicine (ACLAM) and all of whom hold research degrees in addition to DVMs, are charged with ensuring that healthy animals are available for research projects, providing veterinary care as needed, training research staff, and participating in projects requiring veterinary expertise. These veterinarians share emergency-call duty during non-business hours to ensure prompt attention to any animal in need of medical attention.

The Diet Preparation Facility is a well-equipped, large-scale formulation services unit. All animal diets received at NCTR are processed through the Diet Preparation Facility. The majority of dosed diets, dosed water, gavage solutions, and creams used in experiments performed at the Center are prepared in this facility. Dosed-feed production capability is 200,000 kg per year. Diets can be mixed with test articles in solution or solid state in

concentrations as low as 0.1 parts-per-billion. In addition, test articles can be mixed in the animals' drinking water to exacting standards in concentrations as low as one microgram per milliliter.

The Pathology Services group provides support including necropsy and routine histopathology, as well as molecular pathology, immunohistochemistry, clinical pathology, and other nonroutine services such as digital macrophotography, laser capture microdissection, and image archiving using digital storage of microscopic images at diagnostic resolution. The staff includes a professional team of pathologists and specialists in molecular and toxicologic pathology, a medical technologist, and American Society for Clinical Pathology (ASCP)-certified technical support staff.

FY 2008 Accomplishments

Immediate Office

The Division provided oversight and management of all NCTR laboratory animal facilities. Division personnel were responsible for breeding, rearing, and acquiring and quarantining all experimental animals used on-site. Personnel submitted annual reports assuring compliance with federal regulations and National Institutes of Health guidelines relative to our Animal Care and Use Program and participated in semi-annual program reviews, facility inspections, and experimental protocol reviews as part of the NCTR IACUC proceedings. The Division Director is NCTR's Attending Veterinarian and the IACUC Vice-Chair. All animal resource needs were managed for all research projects. Division personnel served as government project officers for pathology services, animal care and diet-preparation services, rodent bedding, and rodent diet contracts. This arrangement ensured coordination of activities and provided essential input associated with IAG and CRADA development, initiation, and completion.

The Veterinary Care program was administered through DVS and, in addition to providing veterinary care and surgical services to NCTR's research animals, included oversight of policies and procedures for animal procurement and transportation, preventive medicine, health and genetic monitoring, environmental enrichment, surgical protocols, anesthesia of laboratory animals, pain management, and euthanasia. Veterinarians also served as Principal Investigators or Co-Investigators on several protocols. All divisional veterinarians were voting members of the IACUC. To ensure state-of-the-art housing environments for research animals, members of this Division played an integral role in planning animal-facility renovation projects, especially the renovation and expansion of the Nonhuman Primate Research Center.

Animal Care/Diet Preparation Services

During FY 2008, contract personnel supported a daily average of 29 experiments. These experiments entailed the daily husbandry services for an average 5451 rodents and 116 rhesus monkeys. In addition, housing, animal care, and technical services were provided for three minipigs for one month. A variety of technical procedures were performed on many experiments, including tattooing, tumor palpations, biological sample collections, injections, oral gavage (including neonatal mice), behavior assessments on rats and

rhesus monkeys, application of topical-dosed creams, rodent breeding operations, quarantine of rodents and rhesus monkeys, physical and pregnancy examinations of rhesus monkeys, microchip implantations, and humane euthanasia. An ongoing AALAS training program ensured the maintenance of a high percentage of certified staff. Currently 85% of animal care and diet-preparation staffs are AALAS-certified, and eight members of the animal care management group are Certified Managers of Animal Resources (CMAR). In addition to processing standard rodent chow (autoclaving, packaging, and delivery), dosed diets, dosed water, and topical creams were prepared to exacting specifications for NTP (National Toxicology Program) experiments. The trend of converting to irradiated diet from autoclavable diet continued in FY 2008. Elimination of all autoclaved rodent diet should be realized by the beginning of FY 2009. Quality-control personnel performed monthly inspections of all animal housing and diet-preparation units, performed hundreds of quality-control audits of animal care and diet-preparation procedures and maintained, updated, and created a large volume of SOPs. An on-site rodent-production operation supplied animals for the majority of experiments. Extensive environmental and health monitoring activities were performed in cooperation with NCTR's microbiological surveillance and chemistry support groups to ensure pathogen exclusion from animal colonies, bedding, and feed.

Pathology and Pathology-Related Services

During FY 2008, the Pathology Services group performed the following services:

- Necropsy of 1,100 animals, several, including 24 juvenile-rhesus monkeys, requiring full-body perfusion and neuropathology workup
- Blood analysis on 2,861 animals including evaluations of hematology, chemistries, RIAs, reticulocytes, spinal fluid, urinalysis, and platelet isolation

In addition to routine pathology services, other accomplishments for FY 2008 include:

- Conducted NTP quality assessment and peer review of pathology data for three chronic bioassay studies. Developed and implemented methods to conduct digital Pathology Working Group (PWG) reviews for the three studies conducted along with the conventional (traditional round table) PWG reviews. The significance of this accomplishment is that it identifies NCTR as the only facility to successfully conduct NTP PWG reviews using digital images
- Provided nonroutine services such as digital macrophotography, laser capture microdissection, and image archiving using digital storage of microscopic images at diagnostic resolution
- Developed and implemented procedures for harvesting articular cartilage and synovial fluid from joints of rats, and for the decalcification of the stifle joints using EDTA (ethylene diamine tetra-acetic acid) to allow the gross trimming of those joints for future immunohistochemistry
- Modified Aperio Image Analysis algorithms for use with Aperio ScanScope to generate high-resolution digital images
- Developed a fully functional bar-coding system that allows the labeling and rapid retrieval of vials that are snap-frozen and stored in a -80°C freezer

- Prepared tissue-microarray blocks and slides using 1.0, 1.5, and 2.0 mm core sizes
- Detected oncoproteins, oncosuppressor proteins, cell-cycle and apoptosis-associated proteins, tumor markers, lymphoid markers, hormones and hormone receptors, growth factors and their receptors, and cell-type markers for immunohistochemistry protocols and performed *in situ* hybridization

FY 2009 Plans

- Continue to support the research mission of NCTR through excellence in animal care, veterinary care, diet preparation, and pathology services
- Continue a quality Laboratory Animal Care and Use Program that is consistent with state and federal laws, regulations, and guidelines
- Play an active role in animal-facility improvement projects including: 1) phases 2 and 3 of the expansion and renovation of the nonhuman primate facility, 2) application of new flooring in the Building 53 cage-processing area, and 3) completion of the new cage-processing rooms in Building 5A
- Expand the swine research program including liaison efforts with Arkansas Children's Hospital in Little Rock, Arkansas
- Expand and improve the environmental-enrichment program for nonhuman primates
- Increase the technical prowess of the animal-care staff to accommodate increasing technical demands of animal-research protocols
- Institute computer-database programs for managing animal-protocol schedules
- Replace the use of stainless-steel canisters with the more ergonomic mobile plastic containers for feed storage in animal rooms
- Develop and implement a Nonhuman Primate Management System to identify and modify practices posing safety concerns
- Develop and implement an internal Quality Assurance Program for the Animal Care/Diet Preparation operation as a supplement to the Quality Control Program
- Continue active participation on research protocols as Principal Investigators and Co-Investigators
- Continue supplying methods development and support, both technical and professional, needed to accomplish the NTP work at NCTR
- Conduct quality assessment and Pathology Working Group for combination drugs for AIDS, acrylamide, and glycidamide as scheduling allows

Contribution to FDA's Strategic Goals

Each research division contributes to FDA's Strategic Goals in its own unique way through the individual and collective talents of its personnel as described in this document. DVS, through its support-services functions and research participation, is part of each division's contribution to these goals. DVS also contributes to NCTR's research program through participation in the projects of other divisions as Principal Investigators and Co-Investigators. Several DVS personnel are DVMs or Ph.D.s whose

specialties in comparative medicine, veterinary pathology, toxicology, genetics, and biochemistry complement the research teams in all other divisions.

The DVS plays a critical support-services role in NCTR's biomedical research program. DVS personnel interact with individuals from every research division on a daily basis, providing expertise in animal care, diet preparation, laboratory-animal medicine, and pathology. These services are provided by highly trained, skilled, and dedicated individuals whose contributions enhance the quality of the research conducted by NCTR scientists. In addition, DVS oversees the NCTR Laboratory Animal Care and Use Program, which has been accredited by the AAALAC since 1977. This distinction assures Center scientists, FDA, and the American consumer that data generated from animal experiments at NCTR are of the highest integrity.

FY 2008 Ongoing Research Projects

NCTR Strategic Goal 1

Advance the scientific approaches and tools to promote personalized nutrition and medicine for the public

PI: Ahn, Young, Ph.D.

Impact of Antimicrobial Residues on the Human Gastrointestinal Tract Microbiota (E0732701)

Responsible Division: Microbiology

Objectives:

- 1) To develop methodology to determine if antimicrobial agent residues bound to fecal contents are microbiologically active
- 2) To evaluate the use of current molecular biology, genomic, and proteomic technologies to determine the impact of antimicrobial agent residues on the human-intestinal microbiota
- 3) To determine the potential of the intestinal microbiota to metabolize antimicrobial residues

PI: Ali, Syed F., Ph.D.

Evaluation of Novel Genetic Changes and Post-Translational Modification in the Protein Products of Specific Genes in Parkinson's Disease and in Substituted Amphetamine Neurotoxicity Using Quantitative Proteome Analysis in Mice Models and Human Subjects (E0712101)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology

Objectives:

- 1) To determine the post-translational protein modifications in the protein extracts of nigral and striatal tissues

in substituted amphetamines and MPTP-treated mice

- 2) To evaluate the effect of various nNOS inhibitors and peroxynitrite decomposition catalysts on the post-translational protein modifications in the protein extracts of nigral and striatal tissues in mice treated with substituted amphetamines and MPTP
- 3) To determine protein-DNA interactions in nuclear extracts from nigral and striatal tissues in mice treated with substituted amphetamines and MPTP for the evaluation of novel post-translational changes in the proteins mediated by various transcription factors
- 4) To determine the effect of various nNOS inhibitors on substituted amphetamine and MPTP-induced free-radical production and monoamine concentrations in mouse brains
- 5) To determine the nitrated protein on tyrosine hydroxylase by immunoprecipitation of tyrosine hydroxylase and co-localization of 3-nitrotyrosine in the presence and absence of nNOS inhibitors to correlate physiological effects with protein changes from objectives 1, 2 and 3
- 6) To determine the post-translational protein modifications in protein extracts and protein-DNA

interactions in nuclear extracts of nigral and striatal tissues obtained from human subjects with Parkinson's Disease

PI: Ali, Syed F., Ph.D.

Neurotoxicity Assessment of Manganese (Mn)-Nanoparticles in PC-12 Cells and in Mice (E0725701)

Responsible Division: Neurotoxicology

Objectives:

- 1) To evaluate the neurotoxicity of different size manganese nanoparticles using PC-12 cultured cells
- 2) To determine if *in vitro* exposure to manganese nanoparticles selectively induces specific genomic changes in PC-12 cultured cells using oligonucleotide microarrays
- 3) To determine if multiple doses of Mn-nanoparticles produce reactive-oxygen species, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), and levels of glutathione in various regions of the mouse brain
- 4) To determine if single or multiple doses of manganese nanoparticles induce specific-genomic changes in various regions of the mouse brain using oligonucleotide microarrays
- 5) To determine if single or multiple doses of Mn-nanoparticles produce significant changes in neurotransmitter concentrations in various regions of the mouse brain
- 6) To determine if single or multiple doses of Mn-nanoparticles produce significant changes in the formation of 3-nitrotyrosine, an *in vivo*

biomarker for oxidative stress, in various regions of the mouse brain
7) To determine if multiple doses of Mn-nanoparticles produce morphological alterations in the brain or visceral organs of the mouse

PI: Ali, Syed F., Ph.D.

Wireless Deep-Brain Stimulation in Nonhuman Primates with MPTP-Induced Parkinson's Disease (E0723801)

External Funding: University of Arkansas—Fayetteville (CRADA)

Responsible Division: Neurotoxicology

Collaborating Division: Office of the Director

Objectives:

- 1) To develop a primate model of Parkinson's disease (PD) using the chemical neurotoxin, MPTP
- 2) To implant microelectrodes within the subthalamus through stereotaxic guidance for Deep-Brain Stimulation (DBS) to:
 - monitor and analyze patterns of tremor and dyskinesia in the PD/MPTP animals wirelessly using smart wireless sensors developed by the University of Arkansas at Fayetteville, Arkansas
 - study patterns of tremor and dyskinesia after DBS treatment in a PD/MPTP animal model
- 3) To evaluate brain neurochemistry, which includes the neurotransmitters dopamine, serotonin, and their metabolites, oxidative stress markers such as reactive-oxygen species (ROS), formation of 3-nitrotyrosine (3-NT), antioxidant enzyme activities, gene expression, transcription factors

associated with dopaminergic neurodegeneration, and post-mortem brain pathology using histochemical techniques

PI: Baek, Songjoon, Ph.D.

Optimal Tree-Based Ensemble Methods for Class Prediction (E0722101)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Divisions: Systems Toxicology, Z-Tech

Objectives:

- 1) To build on the novel Decision Forest classification model developed at NCTR to produce an ensemble of decision trees, each constructed from a different set of predictors by statistically pruning to optimal size using cross-validation
- 2) To use Monte Carlo simulation techniques to compare the performance of the proposed Decision Forest classifiers to the performance of a single optimal decision tree. A primary area of application is the classification of subjects into risk categories in class-prediction problems occurring with genomics and proteomics data

PI: Beger, Richard D., Ph.D.

Analysis of Blood Pyruvate and Valproic Acid Toxicity in Wistar Han Rats in Response to Dietary Carbohydrate and Calorie Restriction with a High Fat, Moderate, and Low Carbohydrate Diet (P00709)

Responsible Division: Systems Toxicology

Collaborating Divisions: Office of Research, Genetic and Reproductive Toxicology, Veterinary Services

Objectives:

To develop an *in vivo* rat model with lower plasma-pyruvate levels by using dietary carbohydrate restriction. Specific aims are:

- 1) To determine whether pyruvate blood levels in CR rats fed a HF/LC (high fat/low carbohydrate) diet are decreased by approximately 30% relative to rats fed a balanced diet
- 2) To determine whether 45% CR Wistar Han rats can adequately survive on a HF/LC diet for several weeks
- 3) To determine whether CR Wistar Han rats fed a HF/LC diet are more susceptible to valproic acid-induced liver injury than rats fed a balanced healthy diet

PI: Beger, Richard

Clinical Metabonomic Biomarkers of Disease and Toxicity (S00643)

Responsible Division: Systems Toxicology

Objective:

To characterize metabonomics signatures found in clinical urine and serum samples seen by 1H NMR and mass spectrometry

PI: Beger, Richard D., Ph.D.

Preclinical Metabonomic Biomarkers of Toxicity and Disease (E0720401)

Responsible Division: Systems Toxicology

Collaborating Division: Neurotoxicology

Collaborating FDA Center: CDER

Objectives:

To examine the utility of metabonomics as an approach to produce predictive models of

cardiovascular, renal, neural, and hepatic toxicity. The models will be built using a variety of pattern-recognition technologies to determine how temporal-endogenous metabolic changes found in NMR or MS spectra of urine, serum, and tissue related to toxicity and disease state

PI: Beland, Frederick A., Ph.D.

Benzocaine-Induced Methemoglobinemia in an Acute Rat Model (E0730201)

Responsible Division: Biochemical Toxicology

Objective:

To produce data that will put the concern about the potential for benzocaine-induced methemoglobinemia in humans consuming meat from benzocaine-treated fish in perspective

PI: Beland, Frederick A., Ph.D.

Carcinogenicity of Acrylamide and its Metabolite, Glycidamide, in Rodents (E0718501)

Responsible Division: Biochemical Toxicology

Objective:

To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice treated neonatally

PI: Beland, Frederick A., Ph.D.

DNA Adducts of Tamoxifen (E0701101)

Responsible Division: Biochemical Toxicology

Objectives:

- 1) To characterize DNA adducts from suspected tamoxifen metabolites

- 2) To develop methods for DNA-adduct detection and quantitation

PI: Beland, Frederick A., Ph.D.

Genotoxicity and Carcinogenicity of Acrylamide and its Metabolite, Glycidamide, in Rodents (E0215001)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Objective:

To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice and Fischer 344 rats treated chronically for two years

PI: Beland, Frederick A., Ph.D.

Liver-Toxicity Biomarkers Study: Phase 1, Entacapone and Tolcapone (E0726601)

External Funding: BG Medicine, Inc. (CRADA)

Responsible Division: Biochemical Toxicology

Collaborating Division: Systems Toxicology

Objective:

To establish liver-toxicity biomarkers and associated algorithms for use in preclinical drug development that will predict the probability of occurrence of hepatocellular injury at any subsequent phase of drug development or following approval of the drug for marketing

PI: Binienda, Zbigniew K., D.V.M., Ph.D.

The Role of Mitochondrial Energy Disruption in the Mechanism of Neurotoxicity: Neurophysiological, Neurochemical, and cDNA Microarray Approaches (E0711001)

Responsible Division: Neurotoxicology,

Collaborating Division: Office of the
Director

Collaborating FDA Center: CFSAN

Objectives:

- 1) To define neurophysiological and neurochemical phenotypes associated with brain exposure to 3-NPA and L-carnitine
- 2) To define changes in patterns of gene expression induced by 3-NPA and L-carnitine in the rat brain
- 3) To assess the attenuation of energy deficits associated with L-carnitine using enzymatic and neurochemical biomarkers of neurotoxicity in the rat model of 3-NPA-induced histotoxic hypoxia
- 4) To establish the relationship between 3-NPA-induced physiological and neurochemical phenotypes and transcriptome profiles in the rat brain model
- 5) To investigate the underlying control mechanisms of dopaminergic activation in mitochondrial dysfunction using 3-NPA and methamphetamine

PI: Boudreau, Mary D., Ph.D.

Bioassays in the Fischer 344 Rat and the B6C3F1 Mouse Administered *Aloe vera* Plant Constituents in the Drinking Water (E0214201)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical
Toxicology

Objective:

To conduct bioassays in rats and mice using standardized preparations of *Aloe vera* to explore the limits of safety for the *Aloe vera*

leaf constituents present in
commercial products

PI: Bowyer, John F., Ph.D.

Further Studies on the Effects of Afmid/TK Deficiencies and Brain, Liver, and Kidney Function (E0726101)

Responsible Division: Neurotoxicology

Collaborating Divisions: Biochemical
Toxicology, Genetic and
Reproductive Toxicology

Objectives:

- 1) To supplement and extend the preliminary histological studies that initially evaluated the changes in the BBB in the Afmid/TK (-/-) mice that occur during the development of pathology
- 2) To begin studies to determine the changes in gene expression that exist prior to the onset of pathology and those that occur during the pathological process and to quantify accompanying behavioral alterations

PI: Chen, James, Ph.D.

Benefit/Risk Classification Models for Regulatory Decision Making in Personalized Medicine (E0722001)

Responsible Division: Personalized
Nutrition and Medicine

Collaborating Division: Genetic and
Reproductive Toxicology

Collaborating FDA Center: CDER

Objective:

To develop prediction models and computational methods for quantitative assessment of benefit/risk models for regulatory decisions in personalized medicine

PI: Chen, James

Modification and Application of Quantitative Risk-Assessment Techniques to FDA-Regulated Products (S00174)

Responsible Division: Personalized Nutrition and Medicine

Collaborating FDA Center(s): CDER, CDRH, CFSAN

Objective:

To conduct cancer and noncancer risk assessments of FDA-regulated products to assist in establishing safest conditions of exposure to toxic substance

PI: Chen, James, Ph.D.

Sex Differences in Molecular Biomarkers for Individualized Treatment of Non-Gender-Specific Disease: A Novel Classification Algorithm for the Development of Genomic Signatures from High-Dimensional Data (E0727901)

Responsible Division: Personalized Nutrition and Medicine

Objectives:

To find sex-specific high-dimensional biomarkers:

- 1) To develop classifiers for each sex using our CERP algorithm as well as several alternative algorithms
- 2) To investigate the improvement in these high-dimensional biomarkers using the variable importance derived from our classification algorithm to prioritize and combine features
- 3) To find optimal cutoffs to select high-dimensional biomarkers and finalize the classification algorithm
- 4) To assess the performance of sex-specific high-dimensional biomarkers from our classification

algorithm by cross-validation to obtain a valid measure of prediction accuracy using publicly available high-dimensional non-gender-specific data

- 5) To develop a user-friendly classification software tool that is downloadable from the Internet

PI: Chen, Tao, Ph.D.

Comparison of Mutation Induction and Types of Mutations in the *cII* Gene of Big Blue[®] Mice Treated with Carcinogens as Neonates and Adults (E0709001)

Responsible Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To determine the mutant frequencies in the *cII* gene of lambda/*lacI*-transgenic mice treated with ethylnitrosourea, a direct-acting carcinogen, and the modifying role of age, sex, and target organ
- 2) To compare the mutant frequencies in the *cII* gene of livers from the transgenic mice exposed as neonates and adults to different doses of aflatoxin B1, a human hepatocarcinogen that requires a metabolic activation
- 3) To determine the effect of exposure of neonatal and adult Big Blue[®] mice to 17- β -estradiol, a human-hormone carcinogen, on subsequent spontaneous and carcinogen-induced mutations in the *cII* gene of the target organs
- 4) To determine the types of *cII* mutations in the mutants from Objectives 1, 2, and 3

PI: Chen, Tao, Ph.D.

DNA-Adduct Formation, Mutations and Patterns of Gene Expression in Big Blue® Rats Treated with the Botanical Carcinogens Riddelliine, Aristolochic Acid (AA), and Comfrey (E0710001)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Divisions: Biochemical Toxicology, Systems Toxicology

Objectives:

- 1) To treat Big Blue® rats subchronically with riddelliine, AA, and comfrey using procedures appropriate for tumor induction
- 2) To analyze DNA-adduct formation in the target tissues for carcinogenesis and in spleen lymphocytes
- 3) To determine the *cII* mutant frequencies and the types of *cII* mutations in the target tissues of treated rats
- 4) To determine global gene-expression patterns in the target and surrogate tissues of treated rats
- 5) To correlate gene-expression patterns with DNA-adduct formation and mutation induction in treated rats

PI: Desai, Varsha, Ph.D.

Development of MitoChip, a Glass-Based Oligonucleotide Microarray Containing Mitochondrial and Nuclear Genes Associated with Mitochondrial Function (E0718601)

Responsible Division: Systems Toxicology

Collaborating Divisions: Biochemical Toxicology, Genetic and Reproductive Toxicology, Neurotoxicology

Collaborating FDA Center: ORA

Objectives:

- 1) To develop a MitoChip containing genes associated with mitochondrial function such as oxidative phosphorylation, β -oxidation of free-fatty acids, tricarboxylic acid cycle, apoptosis, as well as genes involved in the replication, transcription, translation of mitochondrial DNA, DNA repair, and regulation of DNA copy number
- 2) To validate the developed MitoChip by evaluating gene-expression profiles of AZT, an anti-HIV drug, and 3-NPA, neurotoxins known to alter mitochondrial function
- 3) To verify the relative expression levels of differentially expressed genes by real-time quantitative PCR

PI: Desai, Varsha, Ph.D.

Molecular Mechanisms Underlying Gender-Associated Differences in the Adverse Reactions to the Antiretroviral Agent, Zidovudine (AZT): Role of Mitochondrial Toxicity (E0725601)

Responsible Division: Systems Toxicology

Collaborating Divisions: Genetic and Reproductive Toxicology, Personalized Nutrition and Medicine

Objective:

To elucidate molecular mechanisms of mitochondrial dysfunction to address gender-based differences in adverse effects of antiretroviral drugs, such as AZT

PI: Dobrovolsky, Vasily N., Ph.D.

Development of High-Throughput Methodology for Detection of *In Vivo* Mutation in the Endogenous *PIG-A* Gene of Human Blood Cells Using Flow Cytometry (E0728301)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Systems Toxicology

Objectives:

- 1) To design high-throughput methods for detecting *PIG-A* mutant human red and white blood cells by flow-cytometric detection of cells lacking cell-surface protein markers anchored by glycosyl phosphatidyl inositol (e.g., CD59, CD48)
- 2) To use the methods developed in Objective 1 to establish a normal range of *PIG-A* mutant frequencies in red and white blood cells and compare these ranges with those of different groups of human subjects hypothesized to have increased mutational loads
- 3) To compare red blood cell *PIG-A* mutant frequencies determined in Objective 2 with *PIG-A* mutant frequencies in white blood cells from these samples determined by limiting-dilution cloning, and determine the *PIG-A* DNA sequence changes responsible for the white blood cell mutants when the volumes of blood samples permit

PI: Doerge, Daniel R., Ph.D.

Development of a PBPK/PD Model for Acrylamide (E0721201)

External Funding: University of Maryland (CRADA)

Responsible Division: Biochemical Toxicology

Collaborating Divisions: Genetic and Reproductive Toxicology, Personalized Nutrition and Medicine

Objectives:

- 1) To develop a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model for acrylamide and glycidamide
- 2) To determine mutagenicity of acrylamide and its metabolite glycidamide in Big Blue[®] rats
- 3) To determine the DNA-adduct levels and the extent of mutagenicity of furan and its metabolite cis-2-buten-4-diol in neonatal B6C3F1/Tk+/- mice

PI: Doerge, Daniel R., Ph.D.

Genotoxicity, Mutagenicity, and Exposure Biomarkers of Acrylamide and its Metabolite, Glycidamide, in Rodents (E0214601)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To synthesize chemically and characterize spectroscopically the major glycidamide-DNA adducts
- 2) To develop and validate LC-ES/MS/MS assays to quantify the major glycidamide-DNA adducts
- 3) To determine glycidamide-DNA-adduct levels in rodent tissues following short-term exposures of rodents to acrylamide and to glycidamide

- 4) To determine toxicokinetics and compare bioavailability of acrylamide and glycidamide following exposure by intravenous, oral gavage, and dietary administration
- 5) To correlate the levels and kinetics of glycidamide-DNA adducts in target tissues and circulating lymphocytes with acrylamide- and glycidamide-hemoglobin adducts in rodent exposure studies for future use in monitoring human exposure through occupation, smoking, and diet
- 6) To determine *in vivo* mutagenesis of acrylamide and glycidamide using transgenic mice (Big Blue®)

PI: Doerge, Daniel R., Ph.D.

Phytoestrogens and Aging: Dose, Timing, and Tissue (E0721001)

External Funding: University of Illinois (CRADA)

Responsible Division: Biochemical Toxicology

Objective:

To evaluate the potential benefits or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue, and the brain using well-established laboratory animal models

PI: Erickson, Bruce D., Ph.D.

Evaluation of the Mechanisms of Inactivation and Degradation of Third-Generation Cephalosporins by the Bovine-Intestinal Microflora (E0721901)

External Funding: Pfizer, Inc. (CRADA)

Responsible Division: Microbiology

Objectives:

- 1) To evaluate the ability of the bovine-intestinal microflora to inactivate ceftiofur using pure culture isolates and mixed fecal cultures
- 2) To identify primary metabolites of ceftiofur degradation
- 3) To isolate ceftiofur-resistant bacteria and determine the primary mechanisms of drug inactivation
- 4) To investigate the metabolic potential of anaerobic fungi isolated from bovine-fecal samples to degrade ceftiofur
- 5) To compare the metabolism of ceftiofur with the human third-generation cephalosporin, ceftriaxone

PI: Ferguson, Sherry A., Ph.D.

Assessment of Depression Risk Associated with Accutane (13-cis-Retinoic Acid or Isotretinoin) and All-Trans-Retinoic Acid Treatment: Measurement of Behavioral and Neurochemical Alterations in Adult Sprague-Dawley and Flinders Sensitive and Insensitive Line Rats (E0714501)

Responsible Division: Neurotoxicology

Collaborating Divisions: Biochemical Toxicology, Systems Toxicology

Collaborating FDA Centers: CBER, CDER

Objectives:

- 1) To establish the necessary oral doses of 13-cis-retinoic acid and all-trans-retinoic acid in rats that produce peak plasma levels similar to those of humans prescribed 13-cis-retinoic acid
- 2) To measure the toxicity and pathology associated with long-term oral treatment with 13-cis-retinoic acid

acid and all-trans-retinoic acid in rats

- 3) To describe the behavioral alterations associated with chronic 13-cis-retinoic acid and all-trans-retinoic acid treatment in adult male and female Sprague-Dawley rats
- 4) To determine if such alterations resemble those described in humans treated with 13-cis-retinoic acid
- 5) To measure sex differences in behavioral response to 13-cis-retinoic acid and all-trans-retinoic acid treatment
- 6) To evaluate the reversibility of the 13-cis-retinoic acid induced and/or all-trans-retinoic acid-induced alterations
- 7) To assess if genetic predisposition to depression determines the frequency and/or magnitude of the behavioral alterations associated with 13-cis-retinoic acid and/or all-trans-retinoic acid treatment
- 8) To quantitate the neurochemical alterations induced by 13-cis-retinoic acid and/or all-trans-retinoic acid treatment

PI: Ferguson, Sherry A., Ph.D.

Assessment of Specific Cognitive Domains in Girls with a History of Sexual Abuse (E0724701)

Responsible Division: Neurotoxicology

Objective:

To determine if childhood sexual abuse in 8-14 year-old girls has significant effects on cognitive tasks, which measure short-term memory, time perception, learning, color/position discrimination, and motivation, as well as achievement and IQ scores

PI: Ferguson, Sherry A., Ph.D.

Sex Differences in Drug Abuse Susceptibility in Methylphenidate (MPH)-Treated Rats (E0727201)

Responsible Division: Neurotoxicology

Objective:

To determine potential sex differences in substance abuse susceptibility after methylphenidate (Ritalin®) treatment during adolescence

PI: Ferguson, Sherry A., Ph.D.

Training for Bisphenol A Studies (P00706)

Responsible Division: Neurotoxicology

Objectives:

- 1) To develop the appropriate skills and techniques necessary to conduct subsequent studies of developmental treatment with Bisphenol A by training key personnel, including PIs, technicians, and animal-care personnel
- 2) To develop techniques, which include complex behavioral assessments and quantitative volumetric analysis of sexually dimorphic brain regions

PI: Fu, Peter P., Ph.D.

Detection of DNA Adducts in Mice Treated with Benzo[a]pyrene at Low-Exposure Levels (E0723701)

Responsible Division: Biochemical Toxicology

Objective:

To define dose-response curves for benzo[a]pyrene DNA adducts in the A/J mouse

PI: Fu, Peter P., Ph.D.

Method Development for Study of Antioxidant Properties in Dietary Supplement (E0730501)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CFSAN

Objectives:

1) Microsomal Metabolism Mediated Studies:

- To determine if the studied herbal dietary supplements can enhance or inhibit free-radical formation, mediated by microsomal metabolism, in a dose dependent manner
- To determine if the studied herbal dietary supplements can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a dose dependent manner

2) Cell Culture Studies:

- To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS (reactive-oxygen species) concentration, and mitochondrial membrane potential, of the studied herbal dietary supplements in cells, including A549 human-lung carcinoma cells and rabbit-brain rBCECs cells (a normal cell line to assay the toxic effect on CNS)
- To use ESR oximetry technique to determine the inhibition/induction of lipid peroxidation by the studied herbal dietary supplements in A549 human-lung carcinoma cells and rabbit-brain rBCECs cells

PI: Fu, Peter P., Ph.D.

Use of Electron Spin Resonance Spectroscopy to Characterize the Interactions Between Nanoscale Materials and Model Biological Systems (E0730601)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CFSAN

Objectives:

1) Chemical Reactions:

- To determine if nanomaterials can catalyze Fenton reaction to initiate hydroxyl-radical formation in a nanoparticle-size dependent manner
- To determine if nanomaterials and/or their cations can be reduced by natural-reducing agents, such as ascorbic acid and glutathione, leading to the formation of ROS

2) Microsomal Metabolism Mediated Studies:

- To determine if nanomaterials enhance or inhibit free-radical formation, mediated by microsomal metabolism, in a nanoparticle-size dependent manner
- To determine if nanomaterials and/or their cations can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a nanoparticle-size dependent manner

3) Cell Culture Studies:

- To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, of nanomaterials of

different particle size in cells, including A549 human-lung carcinoma cells and rabbit-brain rBCECs cells (a normal cell line to assay the toxic effect on CNS)

- To use ESR oximetry technique to determine the inhibition/induction of lipid peroxidation by nanomaterials of different particle size in A549 human-lung carcinoma cells and rabbit-brain rBCECs cells

PI: Fuscoe, James C., Ph.D.

Assessment of the Global Gene-Expression Changes During the Life Cycle of Rats (E0712201)

Responsible Division: Systems Toxicology

Collaborating Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To use the NCTR rat microarray chip to quantitate the relative expression of approximately 4000 genes in the liver of rats at the following ages: 2, 5, 6, 8, 15, 21, 52, 78, and 104 wks
- 2) To verify the relative-expression levels by quantitative PCR or Northern analysis

PI: Fuscoe, James C., Ph.D.

Systems-Biology Approach to Evaluate Sex Differences in the Heart of a Rat Model (E0723001)

External Funding: Office of Women's Health (OWH)

Responsible Division: Systems Toxicology

Collaborating Divisions: Genetic and Reproductive Toxicology, Personalized Nutrition and Medicine

Objectives:

- 1) To produce a thorough and comprehensive knowledge base of biochemical and molecular sex differences in the hearts of a rat model system
- 2) To interpret these differences in light of sex-related health issues

PI: Gopee, Neera V., Ph.D.

Evaluating the Effects of Over-the-Counter Skin Products, such as Sunscreen, on the Absorption of Dermally Applied Estradiol, in an *In Vitro* and *In Vivo* Model (E0730401)

External Funding: Office of Women's Health (OWH)

Responsible Division: Veterinary Services

Collaborating Divisions: Office of Research, Systems Toxicology

Collaborating FDA Center: CDER

Objectives:

- 1) To investigate the pig as an animal model that will allow the measurement of systemic estradiol when it is applied dermally
- 2) To use the animal model to mimic the clinically reported effects of sunscreen application on estradiol absorption from topically applied estradiol products
- 3) To evaluate factors, such as components in sunscreens or time of application, on the rate and extent of estradiol absorption from dermally applied products
- 4) To develop an *in vitro* system to study and determine the individual components or combination of components in sunscreens responsible for the enhancement in

the absorption of estradiol from topically applied estradiol products

- 5) To use this *in vitro* model to evaluate factors that may impact absorption of estradiol from dermally applied products

PI: Gough, Bobby J.

Developmental and Standardization of a Microdialysis Technique in Mice (P00697)

Responsible Division: Neurotoxicology

Objective:

To develop and standardize an *in vivo* microdialysis technique for the measurement of neurotransmitters in the extracellular fluid of the mouse brain

PI: Guo, Lei, Ph.D.

Differential Gene Expression in Rodent and Human-Primary Hepatocytes Exposed to the Peroxisome Proliferators Activated-Receptor (PPAR)- α Agonists (E0721301)

Responsible Division: Systems Toxicology

Objectives:

- 1) To obtain the global gene-expression patterns response to PPAR- α agonists in rodent and human hepatocytes in both transcriptional and translational levels
- 2) To compare mutual versus species-specific gene-expression response to PPAR- α agonists
- 3) To investigate specific genes regulated by PPAR- α agonists in susceptible species such as rat and mouse compared to human
- 4) To identify novel target genes whose expression has not been

previously reported to be affected by PPAR- α agonists

- 5) To determine whether the expression of candidate target genes is PPAR- α dependent

PI: Hammons, George, Ph.D. J.

Assessment of Interindividual Variability in Expression of DNA Methyltransferases, DNMT3a, and DNMT3b, in Liver and Identification of Factors Influencing Expressions (E0716701)

Responsible Division: Associate Director for Regulatory Activities

Objectives:

- 1) To determine levels of expression of DNMT3a and DNMT3b in liver samples from a pool of donors selected according to smoking status, gender, and age
- 2) To determine the effect of tobacco smoke on DNMT1, 3a, and 3b expression in liver-cell systems
- 3) To assess the polymorphism frequency identified in DNMT3b in the sample pool included in the study and assess whether it is correlated with expression

PI: Hansen, Deborah K., Ph.D.

Mechanism of Biotin Deficiency-Induced Malformations (E0713301)

Responsible Division: Personalized Nutrition and Medicine

Objectives:

- 1) To determine if palatal tissue from biotin-deficient embryos is able to fuse *in vitro* in either biotin-sufficient or deficient medium
- 2) To determine if arachidonic acid increases palatal fusion and improved limb development and increases the length of the long

bones *in vitro* from biotin-deficient mouse embryos

- 3) To determine if prostaglandin E2 increases palatal fusion and improved limb development and increases the length of the long bones *in vitro* from biotin-deficient mouse embryos
- 4) To determine if malonyl CoA increases palatal fusion and improves limb development and increases the length of the long bones *in vitro* from biotin-deficient mouse embryos
- 5) To determine fetal arachidonic acid content and synthesis *in vivo*
- 6) To determine if arachidonic acid is able to prevent biotin deficiency-induced orofacial clefting and limb hypoplasia *in vivo*

PI: Hart, Mark E., Ph.D.

Protective Effect of Vaginal-*Lactobacillus* Species Against *Staphylococcus Aureus*-Mediated Toxic-Shock Syndrome (E0725501)

Responsible Division: Microbiology

Objective:

To determine whether probiotic administration of *Lactobacillus* can thwart *S. aureus* TSST-1 production if supplemented in women's tampons

PI: He, Zhen, Ph.D.

Brain Sexual-Dimorphic Structures and Sex Hormone-like Compounds: Animal Request for Methods Development and Training (P00710)

Responsible Division: Neurotoxicology

Objective:

To explore the utility of a more comprehensive evaluation of the

effects of SHLCs (sex hormone-like compounds)

PI: Heflich, Robert H., Ph.D.

Phosphatidylinositol Glycan—Complementation Group A (*PIG-A*) Mutagenesis: Development of Methods for the Identification and Molecular Characterization of Mutations in the *PIG-A* Gene in Human Lymphoblastoid Cells and C57Bl/6 Mice (E0720901)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Personalized Nutrition and Medicine

Objectives:

- 1) To develop flow-cytometric methods for the detection of cells with mutations in the *PIG-A* gene using wild-type and mutant human lymphoblastoid cells, TK6, and WTK1 as a model
- 2) To develop flow-cytometric methods for the detection of hematopoietic cells with mutations in the *PIG-A* gene in C57Bl/6 mice

PI: Hong, Huixiao, Ph.D.

Baseline Practices for Analyzing Genome-Wide Association Study (GWAS) Data (E0729701)

Responsible Division: Systems Toxicology

Collaborating Divisions: Personalized Nutrition and Medicine, Z-Tech

Collaborating FDA Center: CDER

Objective:

To compare the latest methods for analyzing GWAS data with a focus on developing baseline practices

PI: Kaput, James

Obesity Prevention Summer Program: Feasibility of Implementing a Multi-Component Obesity Prevention Intervention at a Youth Program in the Mississippi Delta (E0729601)

Responsible Division: Personalized Nutrition and Medicine

Objectives:

- 1) To study the complex interaction of genetic makeup and environment—particularly the food environment
- 2) To test the hypothesis that CBPR (community-based participatory research program), coupled with omics research technologies and healthcare, will produce more reliable scientific data and results and, at the same time, improve the lives of the participants through improved knowledge, nutrition, and healthcare

PI: Leakey, Julian E., Ph.D.

Studies of Usnic Acid and *Usnea Barbata* Herb in Fischer 344 Rats and B6C3F1 Mice (E0215911)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Collaborating Division: Systems Toxicology

Collaborating FDA Center: CFSAN

Objective:

To establish appropriate doses of usnic acid and *Usnea Barbata* preparations, administered in feed, in male and female Fischer 344 rats and B6C3f1 mice

PI: Leakey, Julian E., Ph.D.

Subchronic Studies of Usnic Acid in Fischer 344 Rats and B6C3F1 Mice (E0216501)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Objective:

To evaluate the subchronic toxicity of usnic acid in male and female Fischer 344 rats and B6C3F1 mice

PI: Leakey, Julian E., Ph.D.

Subchronic Toxicology Studies of *Usnea Lichen* in Fischer 344 Rats and B6C3F1 Mice (E0216601)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Objective:

To evaluate the subchronic hepatotoxicity of *Usnea Lichen* in male and female Fischer 344 rats and B6C3F mice

PI: Lee, Taewon, Ph.D.

Evaluating the Statistical Significance of Treatments on a Group of Correlated Genes (E0723601)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To investigate the true-significance level and power of statistical methods for combining correlated p-values
- 2) To develop adjustments that eliminate or mitigate the deleterious effect of correlations
- 3) To implement computer algorithms that will efficiently compute

adjusted p-values for the large numbers of subsets defined through a gene ontology

PI: Lyn-Cook, Beverly A., Ph.D.

Correlating Gene Expression with Activity of Chemotherapeutic Agents to Identify the Mechanism of Resistance to Geldanamycin Analogs (E0724101)

Responsible Division: Associate Director for Regulatory Activities

Collaborating Divisions: Biochemical Toxicology, Personalized Nutrition and Medicine

Objectives:

- 1) To identify genes involved in chemoresistance and chemosensitivity to a group of geldanamycin analogs using a pharmacogenomics approach
- 2) To validate the functions of candidate genes in chemoresistance to these geldanamycin compounds
- 3) To reveal the functional network formed by multiple factors that cooperate to mediate cellular resistance to geldanamycin
- 4) To identify novel inhibitors of the chemoresistance genes or therapeutic combinations to avoid the resistance mechanism
- 5) To identify structural features of the geldanamycin analogs associated with their differential relationship with candidate genes using structure-activity analysis

PI: Lyn-Cook, Beverly A., Ph.D.

Genotyping of Transporter Genes Associated with Gender Differences and Promoter Methylation of UGT1A1 in Human Liver: A Means of Assessing Safety and Toxicity of Chemotherapeutic Drugs (E0729801)

External Funding: Office of Women's Health (OWH)

Responsible Division: Associate Director for Regulatory Activities

Collaborating Divisions: Office of Research, Biochemical Toxicology, Personalized Nutrition and Medicine

Collaborating FDA Center: CDER

Objectives:

- 1) To identify polymorphisms in drug-transporter genes identified to be differentially expressed according to gender in human liver samples
- 2) To correlate polymorphism frequencies in male and female to gene expression
- 3) To evaluate the methylation profile of UGT1A1 promoter in human-liver samples from male and female and correlate it to expression of UGT and its activity
- 4) To evaluate effects of polymorphisms in transporter genes on uptake and clearance of chemotherapeutic drugs in a functional assay using the B-CLEAR human *in vitro* model

PI: Lyn-Cook, Beverly A., Ph.D.

Sex Differences in Chemotherapeutic Toxicity: Profiling of Transporter Genes in Human Liver (E0725401)

Responsible Division: Associate Director for Regulatory Activities

Collaborating Divisions: Biochemical Toxicology, Personalized Nutrition and Medicine, Systems Toxicology

Objectives:

- 1) To identify sex differences in the gene expression of drug transporters known to be involved in transport of chemotherapeutic

drugs and with hepatic expression in human liver tissues

- 2) To evaluate sex-related hepatic-drug transport function, including both of the basolateral transport systems that are responsible for translocating drugs across the sinusoidal membrane and the active canalicular transport systems that are responsible for the biliary excretion of drugs using sandwich-cultured human hepatocytes
- 3) To characterize the relationships between transporter-gene expression and uptake or excretion of chemotherapeutic drugs defined with the sandwich model and transporter-transfected cell lines
- 4) To evaluate the effects of sex hormones on hepatic-transporter-gene expression in human-cancer cell lines and sandwich-cultured hepatocytes
- 5) To identify and validate novel transporter-drug correlations using a chemogenomic approach followed by cytotoxicity and drug-uptake studies in cell lines overexpressing specific transporter genes
- 6) To develop an *in silico* pharmacokinetic-modeling program based on the data from sandwich-cultured hepatocytes to predict potential *in vivo* drug pharmacokinetics and toxicity in men and women
- 7) To develop guidelines and recommendations for clinical-trial design and analysis of sex differences in new drug applications

PI: Lyn-Cook, Beverly A., Ph.D.

Sex differences in Systemic Lupus Erythematosus (SLE): Effects of a Single Nucleotide Polymorphism (SNP) in the Prolactin (PRL) Gene on Individual Response to Prasterone Therapy (E0727401)

External Funding: Office of Women's Health (OWH)

Responsible Division: Associate Director for Regulatory Activities

Collaborating Divisions: Biochemical Toxicology, Neurotoxicology, Personalized Nutrition and Medicine, Veterinary Services

Objective:

To elucidate whether the PRL - 1149G SNP increases SLE susceptibility by modulating signal transduction pathways in a manner reversible by prasterone

PI: Mei, Nan, Ph.D.

Development of a New T-cell Receptor (TCR) Gene Rat Model for Safety Screening of Pharmaceuticals and Other Chemicals for Potential Mutagenicity (E0719601)

Responsible Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To develop an *in vivo* model using the *TCR* genes of the Fisher 344 rat for the rapid, cost-effective, and predictable identification of pharmaceuticals and other chemicals that can induce mutations
- 2) To use model mutagens, *N*-ethyl-*N*-nitrosourea (ENU) and cyclophosphamide (CP) to investigate the potential utility of the *TCR* gene mutation assay using

- isolated spleen lymphocytes derived from treated Fisher 344 rats
- 3) To compare the mutant frequencies in the *TCR* genes and the *Hprt* gene in spleen lymphocytes of rats after mutagen exposure to validate the TCR assay

PI: Moore, Martha M., Ph.D.

Further Evaluation of the Types of Genetic Events Detected by the Mouse Lymphoma Assay (MLA) and the Role of the Assay in Mechanistically Based Risk Assessment (E0711701)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Systems Toxicology

Objectives:

- 1) To determine if the L5178Y/TK+/- Mouse Lymphoma Assay adequately detects both aneuploidy and mitotic recombination
- 2) To determine if the L5178Y mouse lymphoma cells have active recombinase functions, which lead to a large proportion of mutants that result from recombinase-mediated rearrangements
- 3) To determine the fundamental genetic mechanism(s) causing the small and large colony thymidine kinase mutant phenotypes

PI: Morris, Suzanne M., Ph.D.

Effect of *p53* Genotype on Gene-Expression Profiles in Mice Exposed to the Model Mutagen, *N*-ethyl-*N*-nitrosourea (ENU) (E0712901)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Divisions: Personalized Nutrition and Medicine, Systems Toxicology

Objectives:

- 1) To determine the effect of mutation in the *p53* tumor-suppressor gene on gene-expression profiles in young and aged mice
- 2) To determine the effect of mutation in *p53* tumor-suppressor gene on gene-expression profiles in young and aged mice exposed to the model mutagen, *N*-ethyl-*N*-nitrosourea

PI: Morris, Suzanne M., Ph.D.

Methods Development for Measurement of Bone Density and Bone Growth in the Rhesus Monkey (*Macaca Mulatta*) (P00700)

Responsible Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To measure bone density and bone growth at 3-month intervals
- 2) To develop methods for the determination of bone density and closure of the growth plate of the NHP

PI: Morris, Suzanne M., Ph.D.

Methods Development for Measurement of Cardiovascular Parameters in the Rhesus Monkey (*Macaca Mulatta*) (P00701)

Responsible Division: Genetic and Reproductive Toxicology

Objectives:

To measure cardiovascular parameters at 3-month intervals utilizing the Life-Shirt system

PI: Ning, Baitang, Ph.D.

Mechanisms of Gender Differences in Aspirin Effects: Metabolizing Enzymes and Therapeutic Targets (E0727101)

External Funding: Office of Women's Health (OWH)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Divisions: Associate Director for Regulatory Activities, Biochemical Toxicology, Systems Toxicology

Objectives:

- 1) To profile gender differences in the mRNA expression and protein production of drug-metabolizing enzymes known to be involved in aspirin metabolisms, using human liver samples from 50 males and 50 females
- 2) To characterize molecular mechanisms of sex hormones (estrogens, progestogens, and androgens) in regulation of the expression of aspirin-metabolizing genes in human ER-positive hepatic-cell line HepG2-ER(+), using biochemical procedures, including DNA-protein binding assay and reporter-construct assay
- 3) To measure sex-hormone modulation of aspirin effect on platelet aggregation and its related biomarkers (COX-1, COX-2, PGE2, TXA2, and LTB4) using human-platelet precursor cells
- 4) To identify sex-hormone modulation of aspirin actions in human endothelial and epithelial cell lines, by measuring prostacyclin dynamics (PGE2, TXA2 and LTB4) and aspirin-targeting enzymes (COXs, NOSs, and LOX) expression
- 5) To evaluate sex -hormonal modulation of response to aspirin in apolipoprotein E-deficient mice

PI: Parsons, Barbara

Cancer Mutations as Biomarkers of Cancer Risk: Human Studies with Implications for Personalized Medicine (E0726501)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division(s): Personalized Nutrition and Medicine

Objectives:

- 1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk
- 2) To compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent to human extrapolation necessary in cancer risk assessment
- 3) To validate a streamlined allele-specific competitive blocker PCR (ACP-PCR) methodology and to develop the methodology necessary to measure oncogene MF (mutant fraction) in cell-free DNA isolated from plasma
- 4) To convey to the regulatory risk assessment community the regulatory significance of the data regarding tumor-associated mutations which have, and will be, generated

PI: Parsons, Barbara L., Ph.D.

Evaluating the Utility of ACB-PCR in Dose-Response Assessment and Mode-of-Action Evaluation (E0726901)

External Funding: CIIT Centers for Health Research (CRADA)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Neurotoxicology

Objectives:

- 1) To further develop, evaluate, and disseminate a new NCTR method, allele-specific competitive blocker-PCR (ACB-PCR)
- 2) To determine whether ACB-PCR measurements of specific oncogenic-base substitutions can be used to inform and improve the dose-response and mode-of-action assessments required in cancer risk assessment

PI: Parsons, Barbara L., Ph.D.

Measurement of Cancer-Associated Gene Mutation in Colon Tumor and Nontumor Tissue (E0716001)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Neurotoxicology

Objectives:

- 1) To determine k-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in colonic ACF, adenomas, and carcinomas; first by DNA sequencing and, if mutation is not detected, then by ACP-PCR
- 2) To determine K-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in tumor-margin samples and tumor-distant, normal-appearing colonic epithelium from colon cancer patients
- 3) To determine K-ras codon 12 GGT to GAT and GGT to GTT mutant frequencies in autopsy samples of colonic epithelium from colon disease-free individuals

PI: Patterson, Tucker A., Ph.D.

Analyses of the Rat Hippocampus via DNA Microarrays and a Novel Antibody Array, Coupled with Laser Capture Microdissection (LCM)—Evaluation of the Effect of Aging on Gene and Protein Expression Associated with Learning (E0713901)

Responsible Division: Neurotoxicology

Objectives:

- 1) To measure gene and protein expression in regions of the hippocampus to determine regional distribution
- 2) To determine the effect of aging on regional distribution of hippocampal proteins in three strains of rats
- 3) To determine if aging, behavioral performance, and alterations in gene and protein expression in the hippocampus are related
- 4) To correlate the differences in gene and protein expression with behavioral performance of young adult and aged rats in a learning task previously shown to be sensitive to changes in protein expression

PI: Patterson, Tucker A., Ph.D.

Pramipexole: Thirty-Week Toxicity Study in Juvenile Rhesus Monkeys Followed by a Twelve-Week Recovery Period: Use of a Nonhuman Primate Model for Studying the Consequences of Long-Term Dopaminergic Receptor Stimulation on Complex Brain Functions Using the NCTR Operant Test Battery (E0725201)

External Funding: Boehringer Ingelheim Pharmaceuticals Inc. (CRADA)

Responsible Division: Neurotoxicology

Objectives:

- 1) To establish acquisition curves for several operant behaviors in juvenile rhesus monkeys during chronic oral exposure to pramipexole and vehicle
- 2) To determine if such exposure results in any significant changes in the acquisition and performance of these operant and other observable behaviors
- 3) To determine if such exposure results in any significant changes in clinical chemistry or ophthalmic parameters
- 4) To determine plasma-distribution profiles and concentrations of pramipexole at various stages of chronic exposure
- 5) To conduct standard postmortem toxicological investigations, including histopathology
- 6) To conduct a focused neuropathological evaluation

PI: Paule, Merle G., Ph.D.

Complex Brain Function in Children as Measured by Performance in the NCTR Operant Test Battery (E0703301)

Responsible Division: Neurotoxicology

Objective:

To measure aspects of learning, short-term-memory and attention, motivation, time perception, and color and position discrimination using a battery of automated tests (games)

PI: Paule, Merle G., Ph.D.

Complex Brain Function Study in Children With and Without Major Depression (E0717701)

Responsible Division: Neurotoxicology

Collaborating Division: Office of Research

Objective:

To determine if children diagnosed with major depression according to the Diagnostic and Statistical of Mental Disorders (DSM-IV) criteria perform differently than children without such a diagnosis on tests of motivation, simple-visual discrimination, timing ability, memory, and learning

PI: Paule, Merle G., Ph.D.

Developmental Neurotoxicity Assessment of Acrylamide in Rats (E0215101)

External Funding: National Toxicology Program (IAG)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology

Objective:

To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous-system integrity throughout life

PI: Paule, Merle G., Ph.D.

Effects of Anxiety on Complex Brain Function in Children (E0721701)

Responsible Division: Neurotoxicology

Objective:

To determine if children with high levels of anxiety perform differently than children without anxiety on tests of motivation, simple visual discriminations, timing ability, memory, and learning

PI: Paule, Merle G., Ph.D.

Evaluation of Changes in Gene Expression in the Brain Associated with Normal Development and the Behavioral Toxicity Caused by Developmental Exposure to the N-Methyl-D-Aspartate (NMDA) Receptor Antagonists, Sodium Channel Blockers, and Combinations (E0716501)

External Funding: Astra Charnwood (CRADA)

Responsible Division: Neurotoxicology

Objectives:

- 1) To determine the differences in gene expression between control and treated subjects from earlier rat studies, which entailed chronic treatment with MK-801, phenytoin, and combinations of the two
- 2) To establish acquisition curves for several operant behaviors performed by rats during chronic oral exposure to ketamine or remacemide
- 3) To determine the differences in gene expression between control subjects and subjects treated with ketamine and remacemide at times during behavioral training and performances that coincide with the expression of treatment-related effects
- 4) To establish "normal" gene-expression profiles during a variety of developmental stages in the Sprague-Dawley rat brain
- 5) To determine the differences in gene expression between control subjects and subjects acutely treated with ketamine during a sensitive brain growth spurt period
- 6) To compare gene expression associated with the ketamine-

induced apoptosis with that expressed later in life after chronic ketamine exposure

PI: Paule, Merle G., Ph.D.

Novel Studies on Sites-of-Action and Mechanisms in Chronic Balance Dysfunction (E0722301)

External Funding: University of Arkansas for Medical Sciences (CRADA)

Responsible Division: Neurotoxicology

Objectives:

- 1) To develop and implement a comprehensive assessment of all levels of the neuraxis in an effort to determine CNS deficits due to balance disorder and vertigo
- 2) To develop and assess strategies to restore those CNS deficits

PI: Pogribny, Igor P., Ph.D.

Global and Locus-Specific DNA Hypomethylation: A Common Mechanism Involved in Genotoxic and Nongenotoxic Rat Hepatocarcinogenesis (E0718101)

Responsible Division: Biochemical Toxicology

Collaborating Divisions: Office of the Director, Genetic and Reproductive Toxicology, Systems Toxicology

Objectives:

- 1) To determine if the temporal alterations in genomic-methylation profile in preneoplastic-liver tissue observed in the folate/methyl-deficient model of rat-endogenous hepatocarcinogenesis also occur in other carcinogenesis models
- 2) To identify genes that are consistently up-regulated or down-regulated in target tissues during

the promotion stage of carcinogenesis

- 3) To evaluate if the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation, is specific only to target tissues and may be used for early detection of chemicals with carcinogenic potential

PI: Rafii, Fatemeh, Ph.D.

Biotransformation of Isoflavonoid Phytoestrogens by Colonic Microfloras of Experimental Animals (E0724401)

Responsible Division: Microbiology

Collaborating Divisions: Biochemical Toxicology, Systems Toxicology

Objective:

To use fecal samples of monkeys and rodents to find out if the metabolites produced by intestinal microfloras of experimental animals exposed to phytoestrogens are the same as those of humans or whether the animal-colonic bacteria metabolize them to different compounds

PI: Schmued, Laurence C., Ph.D.

Histochemical Test Battery for Evaluating the Efficacy and Toxicity of Putative Alzheimer's Disease Therapeutics of FDA Relevance (E0727301)

Responsible Division: Neurotoxicology

Objective:

To test the hypothesis that Alzheimer's Disease (AD), which is characterized by the deposition of insoluble amyloid plaques in the brain, is the result of a cascade of pathological processes and that pharmacological intervention at

various points within this sequence of events could attenuate the resulting pathology

PI: Schmued, Laurence C., Ph.D.

Proteomics of Toxicant-Induced Neuronal Degeneration (E0711101)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology, Systems Toxicology

Objectives:

- 1) To resolve the chemical identity of the endogenous protein(s) associated with neuronal cell death as identified by Fluoro-Jade B binding
- 2) To determine if the same proteins are expressed regardless of the mechanism of neurodegeneration
- 3) To resolve the chemical identity of the fluorescent component in Fluoro-Jade B responsible for the high-affinity labeling of degenerating neurons
- 4) To resolve the metabolic pathway by which the "degeneration protein" is generated

PI: Schnackenberg, Laura

Metabolomic Signatures of Bacterial Contamination in Milk as a Model System (E0732501)

Responsible Division: Systems Toxicology

Collaborating Divisions: Microbiology

Collaborating FDA Center(s): ORA

Objectives:

- 1) To evaluate metabolomic and bacterial signatures of drink spoilage
- 2) To develop a quick screen for a bacterial contamination of drinks due to spoilage that can be applied

for quality-control purposes and to ensure food safety

PI: Tareke, Eden, Ph.D.

The Effects of Acrylamide and PhIP on Normal Human Brain Cortical Neuronal (HCN-1), PC12, and HepG2 Cells *In Vitro*: Activation or Inactivation of Phase I and II Enzymes (E0726301)

Responsible Division: Neurotoxicology

Collaborating Division: Associate
Director for Regulatory Activities

Objectives:

- 1) To determine the effects of acrylamide or PhIP on cell proliferation, transformation, toxicity, apoptosis, and neurotransmitters turnover in HCN-1 and PC12 cells
- 2) To determine the effects of acrylamide or PhIP on the expression of CYP 1A1, 1A2, 1B1, 3A4, and GSTs in HepG2, PC12, and HCN-1 cells
- 3) To determine if the dietary agents, I3C, and sesame seed lignans, modulate the effects of acrylamide or PhIP

PI: Wagner, Robert D., Ph.D.

Gene-Expression Responses of Estrogen-Primed Vaginal-Epithelial Cells (VEC) after Contact with *Lactobacillus* Rhamnosus GR-1, *Lactobacillus* Reuteri RC-14, and the Pathogenic Fungus, *Candida albicans* (E0729401)

External Funding: Office of Women's Health (OWH)

Responsible Division: Microbiology

Objectives:

- 1) To ascertain how VEC respond at the molecular level to contact with *C. albicans*

2) To establish whether probiotic lactobacilli have an effect on VEC resistance to *C. albicans*, and how that effect is mediated

3) To establish if estrogen has an influence on these processes

PI: Wang, Cheng, Ph.D.

Assessment of Ketamine in the Developing Nonhuman Primate (E0718901)

External Funding: National Institute of Child Health and Human Development (NICHD)—Ketamine (IAG)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the
Director, Biochemical Toxicology,
Bionetics Site Management

Collaborating FDA Center: CDER

Objectives:

- 1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis or proliferation
- 2) To determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage
- 3) To determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches
- 4) To determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment

PI: Wang, Cheng, Ph.D.

NMDA Antagonist/GABA (Gamma-Aminobutyric Acid) Agonist-Induced Cell Death in the Developing Rat Brain (E0215501)

External Funding: National Toxicology Program (IAG)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology, Bionetics Site Management

Collaborating FDA Center: CDER

Objectives:

- 1) To screen and evaluate pediatric anesthetic agents
- 2) To determine if a one-time bolus dose or prolonged exposure of the developing rat to NMDA antagonists, GABA agonists alone, or their combinations will induce long-term behavioral deficits, as well as long-lasting pathological changes
- 3) To determine the dose, temporal, and pathophysiological relationships between NMDA antagonist/GABA agonist-induced neurotoxicity and long-term behavioral changes
- 4) To determine the neurotransmitter receptor mechanisms involved in the neuron degeneration and behavioral deficits caused by these agents, particularly the role of altered NMDA-receptor function
- 5) To determine by *in situ* hybridization and immunoblot the relative densities of NMDA receptor NR1, NR2A, and NR2B subunits following anesthetic-drug administration
- 6) To identify mechanisms that could link altered NMDA-receptor function with elevation of superoxide free

radicals in response to anesthetic drug-induced apoptosis

PI: Word, Beverly R.

DNA Methylation is Modulated by Lifestyle Factors and Environmental Agents (P00713)

Responsible Division: Associate Director for Regulatory Activities

Objectives:

- 1) To determine the effect of cigarette smoke condensate on DNA methylation of several genes in lung cells
- 2) To assess the ability of other agents to modulate the effect of CSC (class-specific correlations) on gene DNA methylation, either singularly or in various combinations

PI: Yu, Li-Rong, Ph.D.

Methods for Support of a Functional Proteomics Facility at NCTR (E0713501)

Responsible Division: Systems Toxicology

Objectives:

- 1) To establish and standardize for routine-use procedures for whole cell and subcellular organellar isolation for a variety of tissues
- 2) To develop and standardize specific and sensitive markers of cell type and organellar purity and yield
- 3) To identify, adapt, develop, and standardize appropriate 2D protein separation techniques
- 4) To integrate results of objectives 1-3 to provide front-end components of a functional proteomics facility

NCTR Strategic Goal 2

Develop science-based best-practice standards, guidance, and tools to incorporate translational and applied toxicological advancements into the regulatory decision making process

PI: Ali, Syed F., Ph.D.

Neurotoxicity Assessment of Silver (Ag)-Nanoparticles in PC-12 Cells and in Rats (E0728201)

Responsible Division: Neurotoxicology

Objectives:

- 1) To evaluate the neurotoxicity of different sizes of silver (Ag)-nanoparticles using cultured PC-12 cells
- 2) To determine if *in vitro* exposure to Ag nanoparticles selectively induces specific genomic changes in cultured PC-12 cells using microarrays
- 3) To determine if single or multiple doses of Ag-nanoparticles produce reactive-oxygen species, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in the rat brain
- 4) To determine if single or multiple doses of Ag-nanoparticles induce specific genomic changes in the rat brain as indicated with microarrays
- 5) To determine if single or multiple doses of Ag-nanoparticles produce significant changes in neurotransmitter concentrations in the brain in rat
- 6) To determine if single or multiple doses of Ag-nanoparticles produce significant changes in the formation of 3-nitrotyrosine (3-NT), an *in vivo* biomarker for oxidative stress, in the rat brain

- 7) To determine if multiple doses of Ag-nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat

PI: Beland, Frederick A., Ph.D.

Effect of Urinary pH upon the Nephrotoxicity of a Combined Exposure to Melamine and Cyanuric Acid (E0731501)

Responsible Division: Biochemical Toxicology

Objective:

To determine the effect of urinary pH upon the renal toxicities elicited by a combined exposure of melamine and cyanuric acid

PI: Beland, Frederick A., Ph.D.

Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmission of HIV (E0214111)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating Division: Genetic and Reproductive Toxicology

Objective:

To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally, perinatally, or neonatally

PI: Boudreau, Mary D., Ph.D.

Effect of Topically Applied Skin Creams Containing Retinyl Palmitate on the Photocarcinogenicity of Simulated-Solar Light (SSL) in SKH-1 Mice (E0214301)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating Divisions: Office of Research, Regulatory Compliance and Risk Management

Collaborating FDA Center: CFSAN

Objective:

To study the effects of topically applied skin cream containing retinyl palmitate on the photocarcinogenicity of SSL in SKH-1 mice

PI: Boudreau, Mary D., Ph.D.

Effects of *Aloe vera* Components on Cell Proliferation and DNA-Adduct Formation in SKH-1 Mice Following Simulated-Solar Light (SSL) Exposure (E0214001)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating Division: Office of Research

Objectives:

- 1) To determine the dose response and acute kinetics of topical exposure to *Aloe vera* plant components on the structure of SKH-1 mouse skin in the absence of SSL exposure
- 2) To determine the effects of topical exposure of *Aloe vera* plant components on the amount of SSL

required to induce skin edema in the SKH-1 mouse

- 3) To determine the subchronic effects of repeated co-exposure to *Aloe vera* plant components and SSL on skin-cell edema, proliferation, and DNA damage in the SKH-1 mouse
- 4) To determine the tumor-promoting activities of *Aloe vera* plant components following SSL tumor initiation
- 5) To determine the influence of *Aloe vera* components on SSL-induced tumor formations in mice

PI: Buzatu, Dan A., Ph.D.

Analysis of Proton MRS Data Using a Distributed Artificial Neural Network (E0719501)

Responsible Division: Systems Toxicology

Collaborating Division: Personalized Nutrition and Medicine

Objective:

To evaluate if a self-optimizing, parallel-distributed neural network can use the data from *in vivo* proton magnetic resonance spectroscopy (MRS) exams to provide additional information about a brain lesion

PI: Cerniglia, Carl E., Ph.D.

Proteomic Approaches to Elucidate Biodegradative Pathways (E0711801)

Responsible Division: Microbiology

Collaborating Division: Z-Tech

Objectives:

- 1) To use a proteomic approach to isolate putative-catabolic proteins that are over-expressed when microorganisms are grown in the presence of polycyclic-aromatic hydrocarbons

- 2) To develop software to analyze 2D gels

PI: Chen, Huizhong, Ph.D.

Assessment of Effects and Metabolism of Synthetic Azo Colorants Used in Women's Cosmetics on Human Skin Microbiota (E0729301)

External Funding: Office of Women's Health (OWH)

Responsible Division: Microbiology

Collaborating Division: Personalized Nutrition and Medicine

Objectives:

To evaluate the metabolism and effect of color additives used in cosmetics on the skin microbiota with a potential to adversely affect women's health. Specific objectives are:

- 1) To assess the degradability of the synthetic azo colorants in cosmetics by skin bacteria
- 2) To identify and quantify the potential carcinogenic and toxic aromatic amines in the metabolites
- 3) To elucidate the role of the microflora with potential genotoxic effects of cosmetic azo dyes on women's health
- 4) To determine physicochemical properties of the azo dye degrading enzymes from the skin bacteria
- 5) To establish a standardized assay to determine the reductive capacity of the skin microflora on the azo colorants

PI: Delclos, Kenneth (Barry), Ph.D.

Di(2-ethylhexyl)phthalate (DEHP) Toxicokinetics in Neonatal Male Rhesus Monkeys Following Intravenous and Oral Dosing (E0216001)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CBER

Objectives:

- 1) To quantify the metabolism and disposition of multiple, single-intravenous doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks
- 2) To quantify the metabolism and disposition of multiple, single-oral doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks
- 3) To use the results to evaluate the feasibility and utility of a subchronic toxicity study of DEHP
- 4) To utilize blood and testicular tissue from infant monkeys to establish methods to be utilized in the subchronic study or estimate variability in the endpoints to aid in determining the number of animals required in each dose group for a subchronic study

PI: Delclos, Kenneth (Barry), Ph.D.

Dietary Modulation of the Renal Toxicity of *p*-nonylphenol (NP) and Di(2-ethylhexyl)phthalate (DEHP) (E0714201)

Responsible Division: Biochemical Toxicology

Objectives:

- 1) To demonstrate that the cystic kidney disease, previously shown to

be induced by *p*-nonylphenol in developing NCTR CD rats fed a soy-free diet, is decreased in incidence or severity in rats fed soy-containing diets

- 2) To evaluate the renal toxicity of dietary DEHP in developing rats maintained on a soy-free diet
- 3) To evaluate potential early markers of renal cystogenesis in *p*-nonylphenol- and DEHP-treated rats and their modulation by soy-containing diets
- 4) To evaluate the roles of modulation of antioxidant defenses and cyclooxygenase activities in the protective effect of soy against *p*-nonylphenol- and, if demonstrated, DEHP-induced renal toxicity
- 5) To assess the effect of diet on hepatic, testicular, and lung toxicity of DEHP

PI: Delclos, Kenneth (Barry), Ph.D.

Effects of Sedatives on the Metabolism of Di(2-ethylhexyl)phthalate (DEHP) Administered by Intravenous Injection and the Relationship of DEHP Metabolism to Biological Effects in Neonatal Rats (E0216201)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating FDA Centers: CBER, CDRH

Objectives:

- 1) To determine if sedatives potentially useful for intravenous injection studies of DEHP in neonatal rhesus monkeys, or in common use in neonatal intensive care units (NICU), affect the metabolic profile of DEHP

- 2) To examine DEHP metabolism in neonatal rodents dosed intravenously and orally and relate this metabolism to biological effects

PI: Delclos, Kenneth (Barry), Ph.D.

p-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations (E0213501)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical Toxicology

Collaborating Division: Office of Research

Objectives:

- 1) To determine the effects of *p*-nonylphenol on reproduction and on the development of reproductive and selected other hormone-sensitive organs when administered to CD rats over multiple generations
- 2) To determine if subtle effects observed in the dose range-finding study are magnified through multiple generations
- 3) To evaluate the reversibility of any observed effects

PI: Doerge, Daniel R., Ph.D.

Ketamine Pharmacokinetics in Children (E0726201)

External Funding: University of Arkansas for Medical Sciences (CRADA)

Responsible Division: Biochemical Toxicology

Collaborating Division: Neurotoxicology

Objective:

To develop and validate a sensitive LC/MS/MS method to quantify the enantiomers of ketamine and nor-ketamine in plasma from children

dosed with racemic ketamine during surgical procedures

PI: Doerge, Daniel R., Ph.D.

The Role of Perinatal Development on Toxicokinetics of Bisphenol A (E0216701)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CDRH

Objectives:

- 1) To determine Bisphenol A (BPA) pharmacokinetics at low dose (100 µg/kg bw single dose; 100 µg/kg bw/d repeated)
- 2) To measure free and conjugated forms of BPA separately
- 3) To use deuterium-labeled BPA to avoid issues of background contamination
- 4) To use LC/MS/MS for sensitivity and selectivity of measurement
- 5) To determine complete rat dataset for blood, tissue, and excreta across stages of development (pregnant females, fetuses, neonates)
- 6) To determine BPA pharmacokinetics from oral and intravenous administration in pregnant, lactating, nonpregnant female rats, and neonatal rats
- 7) To determine plasma and urinary pharmacokinetic data in neonatal and adult monkeys
- 8) To use the new pharmacokinetic data in conjunction with literature data from experimental animals and humans to build a physiologically based pharmacokinetic (PBPK) model for BPA

PI: Ferguson, Sherry A., Ph.D.

Long-Term Effects of Morphine Treatment in Preterm Infants Exposed to Repetitive Neonatal Pain (E0724301)

Responsible Division: Neurotoxicology

Objective:

To determine if Neonatal Intensive Care Unit morphine treatment in preterm infants is associated with long-term alterations in short-term memory or motivation at approximately 6 years of age

PI: Gamboa Da Costa, Goncalo, Ph.D.

Assessment of the Nephrotoxicity of a Seven-Day Combined-Exposure to Melamine and Cyanuric Acid (E0731701)

Responsible Division: Biochemical Toxicology

Collaborating Division: Microbiology

Objective:

To investigate the nephrotoxic effect of a seven-day co-exposure to melamine and cyanuric acid in Fischer 344 rats

PI: Hansen, Deborah K., Ph.D.

Developmental Toxicity of Bitter Orange in Rats (E0214701)

External Funding: National Toxicology Program (IAG)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Division: Genetic and Reproductive Toxicology

Collaborating FDA Center: CFSAN

Objective:

To determine potential developmental toxicity of synthetic synephrine and citrus *aurantium* extract in rats

PI: Hansen, Deborah K., Ph.D.

Examination of Embryonic Gene Expression During Neural-Tube Closure (E0710901)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Division: Genetic and Reproductive Toxicology

Objectives:

- 1) To construct SAGE (Serial Analysis of Gene Expression) library of expressed genes from control-untreated gestation day 8.0 and GD 8.25 CD-1 mouse embryos
- 2) To construct SAGE library of expressed genes from GD 3.25 CD-1 mouse embryos treated with a teratogenic dose of valproic acid on GD 8.0
- 3) To compare the libraries to determine which genes are up- or down-regulated by valproic acid treatment
- 4) To use Northern-blot techniques to determine if the mRNA transcripts for these genes are indeed increased or decreased in expression compared to control embryos
- 5) To use Northern-blot techniques to determine a time-course of altered gene expression for genes of interest
- 6) To examine expression of some of these genes after treatment with teratogenic or non-teratogenic doses of valproic acid, valproate analogs, or another developmental toxicant
- 7) To use *in situ* hybridization, laser capture microdissection, and Northern-blot techniques to determine if altered gene expression

is specific for subsets of embryonic cells

PI: Hansen, Deborah K., Ph.D.

Physiological Effects of Bitter Orange in Rats (E0214901)

External Funding: National Toxicology Program (IAG)

Responsible Division: Personalized Nutrition and Medicine

Collaborating Divisions: Biochemical Toxicology, Genetic and Reproductive Toxicology, TPA Pathology Contract

Collaborating FDA Center: CFSAN

Objective:

To determine potential physiological effects of synthetic synephrine as well as an extract from the botanical citrus *aurantium* alone and in combination with caffeine in rats

PI: Howard, Paul C., Ph.D.

Methodology for Safety Testing of Pigments Used for Tattooing, Including Permanent Makeup (E0710501)

Responsible Division: Office of Research

Collaborating Division: Biochemical Toxicology

Objectives:

- 1) To determine the chemicals in tattoo pigments and their metabolism *in vitro*
- 2) To develop methodology for tattooing SKH-1 hairless mice in a quantitative and reproducible manner
- 3) To determine the extent of inflammation induced by the implanted pigment and determine the time of recovery following tattooing
- 4) To determine the acute toxicity of several tattoo inks and permanent

makeup inks in SKH-1 hairless mice in the presence and absence of simulated-solar light

- 5) To determine if tattoo pigments are photocarcinogenic in the SKH-1 hairless mouse using simulated-solar light

PI: Howard, Paul C., Ph.D.

Skin Penetration, Phototoxicity, and Photocarcinogenicity of Nanoscale Oxides of Titanium and Zinc using Quantum Dot (QDOT) (E0215611)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Collaborating Division: Veterinary Services

Collaborating FDA Center: CFSAN

Objective:

To investigate the penetration of QDOTS into the skin of SKH-1 mice

PI: Howard, Paul C., Ph.D.

The Immunogenicity of Permanent Makeup Inks and Their Components (E0216101)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Collaborating Division: Veterinary Services

Objective:

To determine the immunogenicity of permanent makeup inks using a modified LNPA (lymph node proliferation assay) protocol

PI: Leakey, Julian E., Ph.D.

Subchronic Toxicity Studies of Chondroitin Sulfate and Glucosamine in Fischer 344 Rats and Diabetic Goto-Kakizaki Rats (E0215701)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Objectives:

- 1) To investigate the potential toxicity of chondroitin sulfate and glucosamine, administered by oral gavage in male rats
- 2) To determine whether subchronic exposure of glucosamine or chondroitin sulfate potentiate the pathological effects of noninsulin-dependent diabetes in obese-diabetic rats

PI: Leakey, Julian E., Ph.D.

Toxicity Studies of Combination of AIDS Drugs in *p53* (+/-) Transgenic Mice (E0215201)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Collaborating Division: Biochemical Toxicology

Objective:

To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to AIDS drugs, Zidovudine (AZT) and Lamivudine (3TC) in C57BL/6(N5)trp53 (+/-) haplodeficient F1 transgenic mice

PI: Lewis, Sherry M., Ph.D.

Maintenance of the Transgenic *p16/p19*(-/-) Haplodeficient Breeding Colony for Subsequent NTP Protocol Development (E0216301)

External Funding: National Toxicology Program (IAG)

Responsible Division: Office of Research

Objective:

To provide support to maintain the *p16/p19*(-/-) breeding colony [NCTR

code, 7V] at NCTR for use in future NTP protocols

PI: Manjanatha, Mugimane G., Ph.D.

Evaluation of the Genotoxicity and Pharmacokinetics of Methylphenidate in Male Big Blue® Mice (E0723501)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology, Personalized Nutrition and Medicine

Objectives:

- 1) To determine the metabolites of methylphenidate at early times after exposure in B6C3F1 mice to compare the major metabolites in the human, monkey, and mouse
- 2) To determine the plasma levels of methylphenidate and its major metabolites in the B6C3F1 mouse after 28 days of exposure
- 3) To determine the effect of exposure to methylphenidate on body and organ weights of the B6C3F1 mouse after 28 days of exposure
- 4) To determine if long-term exposure to methylphenidate results in a dose-responsive increase in the liver *c11* gene mutant frequency of Big Blue® mouse
- 5) To determine the pharmacokinetics of methylphenidate and its major metabolite, ritalinic acid, in B6C3Fa mice

PI: Mckinzie, Page B., Ph.D.

ACB-PCR Measurement of Azoxymethane-Induced Rat K-ras codon 12 GGT→GAT and GTT→GTT Mutations in Colonic Aberrant Crypt Foci Isolated using Laser Capture Microdissection (E0714901)

Responsible Division: Genetic and Reproductive Toxicology

Objective:

To use PCR-based methods to quantify the rat K-ras codon 12 GGT→GAT and GGT→GTT mutant fractions in rat colonic mucosa, aberrant crypt foci, and tumors at specified times after colon tumor initiation by azoxymethane treatment

PI: Moore, Martha M., Ph.D.

Evaluation of the Ability of the Agar and Microwell Versions of the Mouse Lymphoma Assay (MLA) to Optimally Detect the Mutagenic Potential and Potency of Complex Chemical Mixtures (E0728401)

External Funding: Centers for Disease Control—Mouse Lymphoma Assay (IAG)

Responsible Division: Genetic and Reproductive Toxicology

Objective:

To develop science-based best practice standard and tools to incorporate translational and applied toxicological advancements into the regulatory science process to create a seamless bench-to-bedside continuum

PI: Morris, Suzanne M., Ph.D.

Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys (*Macaca Mulatta*) (E0723401)

External Funding: National Institutes of Health/ National Institute for Child Health and Human Development (NIH/NICHD)—Methylphenidate in Rhesus Monkey and Big Blue® Mice (IAG)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology, Bionetics Site Management, Neurotoxicology, Personalized Nutrition and Medicine

Objectives:

- 1) To determine the baseline frequency of measures of genetic damage in a population of juvenile rhesus monkeys
- 2) To determine the frequency of these measures of genetic damage in a population of juvenile rhesus monkeys at defined intervals during a chronic exposure to methylphenidate
- 3) To determine if chronic exposure to methylphenidate results in measurable effects on the behavior of juvenile rhesus monkeys utilizing the NCTR Operant Test Battery
- 4) To determine the plasma concentration of methylphenidate and its major metabolite, ritalinic acid, during the chronic exposure of juvenile rhesus monkeys to the drug

PI: Morris, Suzanne M., Ph.D.

Evaluation of Growth and Pubertal Development in Male Rhesus Monkeys (*Macaca Mulatta*) Chronically Exposed to Methylphenidate Hydrochloride (MPH) (E0728701)

External Funding: National Institute for Child Health and Human Development (NICHD)—Methylphenidate (IAG)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Divisions: Office of the Director, Biochemical Toxicology, Neurotoxicology, Personalized Nutrition and Medicine, Veterinary Services

Objective:

To evaluate pharmacokinetics and operant behavior testing changes in post-pubertal rhesus monkeys

PI: Parsons, Barbara L., Ph.D.

Analysis of *p53* Codon 270 CGT to TGT Mutation in Simulated-Solar Light (SSL)-Induced Skin Tumors and Exposed Mouse Skin (E0715201)

Responsible Division: Genetic and Reproductive Toxicology

Collaborating Division: Office of Research

Objectives:

- 1) To develop the ACB-PCR detection of mouse *p53* codon 270 CGT->TGT mutation
- 2) To measure the frequency of detection and levels of this mutation in mouse skin tumors
- 3) To measure the frequency of this mutation in skin tissue from tumor-bearing animals
- 4) To measure the frequency of this mutation in skin exposed to decreasing levels of SSL

PI: Paule, Merle G., Ph.D.

Cognitive Assessments of Several Psychotropic Compounds Using the NCTR Operant Test Battery (OTB) (E0721101)

External Funding: Pfizer, Inc. (CRADA)

Responsible Division: Neurotoxicology

Objectives:

- 1) To determine the acute dose-effect relationships of several psychotropic drugs on a battery of operant-behavioral tasks in rhesus monkeys
- 2) To characterize the relative sensitivities of the various behavioral endpoints in NCTR's OTB to these agents
- 3) To compare the behavioral profiles of these agents to those of a variety of reference compounds with well-characterized mechanisms-of-action

PI: Shi, Leming B., Ph.D.

MicroArray Quality Control (MAQC) Project Database (S00691)

Responsible Division: Systems Toxicology

Objective:

- 1) To be a collection of microarray data sets and analysis results provided by MAQC participants
- 2) To serve as a critical mechanism for MAQC participants to share and exchange data in developing predictive models

PI: Shi, Leming B., Ph.D.

Phase II of the MicroArray Quality Control Project (MAQC-II) Toward Personalized Medicine (S00705)

Responsible Division: Systems Toxicology

Objective:

- 1) To assess the reliability of microarray-based predictive models (classifiers) for clinical (diagnosis, prognosis, and treatment outcome) and preclinical (toxicogenomics) applications

- 2) To provide consensus recommendations to the microarray community—the critical component of personalized medicine
- 3) To facilitate the appropriate application of microarray data in the discovery, development, and review of FDA-regulated products

PI: Sutherland, John B., Ph.D.

Microbial Degradation of Fluoroquinolone Antimicrobial Agents (E0722701)

Responsible Division: Microbiology

Collaborating Division: Biochemical Toxicology

Objective:

To identify microorganisms that either completely degrade fluoroquinolones or modify the fluoroquinolone molecule so as to reduce its toxicity to bacteria

PI: Tolleson, William H., Ph.D.

Chemical Inactivation of Protein Toxins on Food Contact Surfaces (E0730301)

Responsible Division: Biochemical Toxicology

Collaborating Division: CFSAN

Objectives:

- 1) To identify cleaning/sanitizing treatments that result in elimination and/or inactivation of protein toxins (abrin and ricin) on food-contact surfaces
- 2) To identify surrogate(s) that can be used to study chemical inactivation of abrin or ricin
- 3) To measure the loss of ricin and abrin biological and biochemical activities in the presence of cleaning/sanitizing solutions using RAW264.7 macrophage cytotoxicity

assays and 28S rRNA adenosine N-glycosidase RTqPCR-based enzyme assays

PI: Tolleson, William H., Ph.D.

Photoinduction of Cutaneous Malignant Melanoma in TP-*ras*/ink4A (+/-) Transgenic Mice (E0708901)

Responsible Division: Biochemical Toxicology

Collaborating Division: Office of Research

Objectives:

- 4) To characterize photochemical DNA damage in the skin of TP-*ras*/ink-4a mice exposed to UVA+UVB radiation
- 5) To determine whether cutaneous malignant melanoma can be induced in neonatal TP-*ras* (+) ink4a (+/-) transgenic mice using UVA+UVB radiation
- 6) To identify photochemically induced mutations within the ink4a/p16/CDKN2A and p53 loci in tumor tissues
- 7) To determine if UVA+UVB exposure at an early age creates a greater risk for developing cutaneous melanoma in TP-*ras* (+)ink4a(+/-) mice compared with chronic UVA+UVB exposure of older animals

PI: Wagner, Robert D., Ph.D.

Maintenance of Defined Flora Associated BALB/c and TG26 Mice in Isolators for use in Future Protocols (E0727001)

Responsible Division: Microbiology

Objective:

To maintain a colony of defined-microbiota BALB/c and Tg26 mice in gnotobiotic isolators between approved protocols

PI: Wang, Cheng, Ph.D.

Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate (E0728501)

External Funding: National Institute for Child Health and Human Development (NICHD)—Gaseous Anesthetics (IAG)

Responsible Division: Neurotoxicology

Collaborating Division: Office of the Director

Objectives:

- 1) To evaluate dose-response effects of gaseous anesthetics:
 - to determine if prolonged exposure to nitrous oxide or isoflurane alone will result in an increase in neuronal cell death
 - to determine if combinations of nitrous oxide and isoflurane will prevent or enhance each other's effects on the developing nonhuman primate
- 2) To determine if a relative high-dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits, as well as long-lasting pathological changes
- 3) To determine, using noninvasive imaging techniques [High resolution dedicated positron emission tomography (microPET) and MRI], if a high-dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or in combination will induce long-lasting pathological changes
- 4) To identify potential underlying mechanisms that could link alteration of mitochondrial function and elevation of reactive-oxygen

species (ROS) to gaseous anesthetic-induced neuronal cell death. L-carnitine will be used to attenuate neurological brain injury associated with mitochondria-related degenerative effects induced by gaseous anesthetics in the developing nonhuman primate

PI: Wang, Cheng, Ph.D.

Methods Development for High-Resolution Dedicated Positron Emission Tomography (microPET) to Rodent Neuroplasticity and Toxicity During Development (E0726401)

Responsible Division: Neurotoxicology

Collaborating Divisions: Office of the Director, Bionetics Site Management

Objectives:

- 1) To use microPET to screen and evaluate *in vitro* and *in vivo* measurements from a broad range of pathophysiological or pharmacological parameters using specific tracers in the developing rat
- 2) To elucidate the relationship between apoptosis-identifying ligands (specific tracers) and subsequent behavioral deficits

NCTR Strategic Goal 3

Conduct research and develop strategic technologies to protect the food supply

PI: Buzatu, Dan A., Ph.D.

FERN (Food Emergency Response Network) Level-One Validation Study of a Mobile, Field-Rugged Rapid Detection and Enumeration System for *Salmonella* in Foods (E0731601)

Responsible Division: Systems
Toxicology

Collaborating Division: Microbiology

Objective:

To conduct a FERN level-one validation for LITMUS Rapid Identification of Bacterial Pathogens (RAPID-B) screening of viable pathogens in food

PI: Buzatu, Dan A., Ph.D.

The Development of Novel Nanotube-Based Technologies that Benefit Public Health, Protect the Public, Produce High-Efficiency Separations and Filtration, and Improve Energetic Material Therapeutics (E0720501)

Responsible Division: Systems
Toxicology

Collaborating Division: Biochemical
Toxicology

Objectives:

To take advantage of the unique physical and electrical properties of nanotubes to develop:

- 1) Novel technologies for the filtration of chemical and biological hazards from air, water, blood, and other media
- 2) Technologies that protect public health or otherwise benefit the public

- 3) Novel nanotube/monoclonal antibody-based cancer therapies

PI: Buzatu, Dan A., Ph.D.

The Development of Rapid Spectral-Based Pathogen Identification Methods for Food Defense and Counter-Bioterrorism (E0714601)

Responsible Division: Systems
Toxicology

Collaborating Division: Office of Operations/Office of Information Management/Office of Information Technology

Objective:

To develop the necessary computational capability to enable the rapid identification of pathogen or nonpathogen microorganisms, nonbiological hoax materials, and mixtures of all mentioned collected real-world situations

PI: Doerge, Daniel R., Ph.D.

Determination of Carcinogenic Mechanisms for Furan in Fischer 344 Rats (E0216401)

External Funding: National Toxicology Program (IAG)

Responsible Division: Biochemical
Toxicology

Collaborating Division: Genetic and Reproductive Tox

Objectives:

- 1) To develop and validate LC-ES/MS/MS assays to quantify the major furan-derived DNA adducts in liver, the major furan-derived hemoglobin adduct(s), and the

- major furan-derived urinary glutathione-derived metabolite
- 2) To determine dose-response relationships for liver furan-derived DNA and hemoglobin adduct formation and repair turnover and the major furan-derived urinary glutathione-derived metabolite in male and female Fischer 344 rats following single and multiple dose exposures of rodents to furan
 - 3) To determine concentration of furan in irradiated NIH-31 diet using headspace-GC/MS
 - 4) To determine toxicokinetics of furan in male and female Fischer 344 rats following exposure by single gavage administration using headspace-GC/MS
 - 5) To combine all data from single- and repeated-dose toxicokinetics of furan in rat blood and liver with the corresponding levels of liver-DNA adducts, hemoglobin adducts, and urinary mercapturates to construct a PBPK model for future use in determining carcinogenic risks from human exposure to furan through the diet
 - 6) To determine mutagenicity of furan in liver *in vivo* using male Big Blue[®] rats
 - 7) To determine the dose-response relationships for furan-mediated hepatotoxicity and cell proliferation in liver of male and female Fischer 344 rats
 - 8) To determine effects of furan on methylation status in rat liver and kidney DNA and histones as epigenetic changes related to carcinogenic process

PI: Khan, Ashraf A., Ph.D.

Molecular Characterization of *Salmonella* spp. and *Vibrio* spp. Isolated from Seafood and Development of Microarray Detection Method (E0720801)

Responsible Division: Microbiology

Collaborating FDA Center: ORA

Objective:

To characterize representative isolates of *Salmonella* and *Vibrio* spp. by molecular techniques, such as pulsed-field gel electrophoresis (PFGE), multilocus sequencing, ERIC (enterobacterial repetitive intergenic consensus), and REP-PCR (repetitive extragenic palindromic-PCR) methods

PI: Khan, Saeed A., Ph.D.

The Survival of *Bacillus Anthracis* in Processed Liquid Eggs (E0725101)

Responsible Division: Microbiology

Objectives:

- 1) To determine the lag-phase duration (LPD), growth rate (GR), and maximum population density (MPD) of *B. anthracis* Sterne strain at different temperatures used for storing and cooking liquid eggs
- 2) To identify inactivation kinetics of spores of Sterne strain at different temperatures

PI: Melchior, William B., Ph.D.

Real-Time PCR Assays for Ricin and Related Potential Bioterrorism Agents in Foods (P00684)

Responsible Division: Biochemical Toxicology

Objectives:

- 1) To develop the materials and methods needed to perform the proposed assays
- 2) To prove that the assays work simply, rapidly, and reliably
- 3) To prove that the assays function as desired in real-world situations, such as with contaminated food stuffs

PI: Melvin, Cathy

Clostridium-Botulinum Toxin Bioassay—
Determination of Human Health Hazard
in Regulatory-Food Samples (E0725901)

Responsible Division: Veterinary
Services

Collaborating Division: Regulatory
Compliance and Risk Management

Collaborating FDA Center: ORA

Objective:

To conduct a mouse bioassay to
detect *Clostridium-botulinum* toxins
in food or other sources that may
affect human health

PI: Melvin, Cathy, Ph.D.

Paralytic Shellfish Toxin Bioassay—
Determination of Human Health Hazard
(E0725801)

Responsible Division: Veterinary
Services

Collaborating FDA Center: ORA

Objective:

To conduct a mouse bioassay to
detect paralytic shellfish toxins in
food or other sources that may
affect human health

PI: Nawaz, Mohamed S., Ph.D.

Isolation and Characterization of
Fluoroquinolone-Resistant Bacteria
from Shrimp (E0730701)

Responsible Division: Microbiology

Collaborating FDA Centers: CVM, ORA

Objectives:

- 1) To isolate and identify
fluoroquinolone-resistant Gram
negative bacteria from shrimp
imported from different countries
- 2) To perform molecular
characterization of
fluoroquinolone-resistant
determinants
- 3) To perform molecular typing of
fluoroquinolone-resistant bacteria

PI: Nayak, Rajesh R., Ph.D.

Antimicrobial-Resistance Genetics of
Emerging *Salmonella Enterica* Serovar
Javiana Phenotypes Involved in Clinical
and Food-Related Outbreaks
(E0726701)

Responsible Division: Microbiology

Objectives:

- 1) To determine the intrinsic resistance
of *Salmonella Javiana* isolates to
multiple antimicrobials by the
SensiTitre[®] antimicrobial-
susceptibility testing protocol using
the Clinical and Laboratory
Standards Institute (CLSI) guidelines
- 2) To determine the variation in
genetic clonality among the drug-
resistance genotypes by fingerprints
the bacteria using the CDC's
PulseNet pulsed-field gel
electrophoresis (PFGE) protocol
- 3) To identify the genes in the multiple
antibiotic region of the *Salmonella*
Genomic Island (SGI)-class 1
integron gene cassettes in the
resistant phenotypes
- 4) To detect antimicrobial-resistance
genes in select multi-drug resistant
Javiana isolates by a PCR-based and
microarray biochip methodologies

PI: Tolleson, William H., Ph.D.

Detection of *Staphylococcal Enterotoxin* in Yogurt Products (P00692)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CFSAN

Objective:

To perform analyses of biological samples from a CFSAN laboratory to determine the steady-state levels of IL-2 mRNA and 18S rRNA in each cDNA sample using quantitative real-time PCR technology and compare the abundance of each RNA species using standard procedures used in other NCTR experiments

PI: Tolleson, William H., Ph.D.

Laboratory Studies in Melamine and Cyanuric Acid Biochemical Toxicology (E0729101)

Responsible Division: Biochemical Toxicology

Collaborating Division: Systems Toxicology

Objective:

To determine chemical and biochemical properties of melamine and cyanuric acid that may influence their toxicity and retention as tissue residues

PI: Tolleson, William H., Ph.D.

Thermodynamic Measurements for Inactivation of Bioterrorism Agents Ricin and Abrin (P00708)

Responsible Division: Biochemical Toxicology

Collaborating FDA Center: CFSAN

Objectives:

- 1) To measure forward-rate constants for thermal denaturation of ricin and

abrin at seven temperatures (60, 65, 70, 75, 80, 85, 90, and 95 °C) and three buffer combinations (0.10 M NaCl buffered with 20 mM lactate, pH 3.0; 20 mM acetate, pH 5.0; and 20 mM phosphate, pH 7.0) by monitoring the quenching of intrinsic protein (tryptophan) fluorescence (EX295, EM340) in a thermostatted spectrofluorimeter

- 2) To select time measurement for toxin proteins and measure reverse-rate constants (protein renaturation) at one temperature and one buffer combination
- 3) To calculate K_{eq} and ΔG from ratio of rates
- 4) To determine $T_{\Delta S}$ from ΔG and ΔH
- 5) To determine the influence of solvent pH on isothermal toxin folding/unfolding equilibria
- 1) To identify time-, pH-, and temperature-dependent reversible and irreversible transitions in ricin conformation and correlate these with changes in toxin-dependent enzyme activity and cytotoxicity

PI: Wagner, Robert D., Ph.D.

Mechanistic Evaluation of the Induction of Lymphoproliferation and Apoptosis Inhibition by Probiotic Bacteria in Mice Infected with *Salmonella Enterica* (E0727601)

Responsible Division: Microbiology

Objectives:

- 1) To orally challenge defined human microbiota-associated (HMA) BALB/c mice and probiotic-bacteria-treated HMA BALB/c mice with *Salmonella enterica* and isolate intestinal mucosal-associated lymphoid tissues (MALT), including:

- Peyer's patches, lamina propria, and mesenteric lymph nodes
- 2) To use pathway-focused gene-expression profiles generated from real-time PCR expression arrays to compare signal transduction in MALT from HMA mice treated with or without probiotic bacteria and orally challenged with *S. enterica*
 - 3) To develop immunohistochemical (IHC) and *in situ* hybridization (ISH) conditions to detect the expression of the signal-pathway molecules implicated in activation and apoptosis inhibition in mucosal T-cells and accessory cells in tissue sections of Peyer's patches, lamina propria, and mesenteric lymph nodes
 - 4) To conduct IHC and ISH studies on tissue sections for detection of molecules involved in the regulation of lymphocyte activation and programmed cell-death pathways induced by bacterial surface antigens
 - 5) To compare the probiotic-treated and untreated mice for expression of dendritic cell, macrophage, and IEC-derived cytokines
- 2) To demonstrate its utility in simulated counterterror and food defense

PI: Wilkes, Jon G., Ph.D.

Rapid Bacterial Identification with Subspecies-Level Specificity (E0714701)

Responsible Division: Systems
Toxicology

Collaborating Division: Microbiology

Collaborating FDA Center: CFSAN

Objective:

- 1) To develop a complete instrumental or computational system for rapid-bacterial identification at the subspecies level

NCTR Strategic Goal 4

Conduct bioinformatics research and development in support of FDA's regulatory mission

PI: Tong, Weida, Ph.D.

Development of ArrayTrack™ Modules to Link Functionality of ArrayTrack™ with SAS Scientific Discovery Solutions (SDS) (E0721401)

External Funding: SAS Institutes, Inc. (CRADA)

Responsible Division: Systems
Toxicology

Objective:

To develop modules in ArrayTrack™ that integrate the functionalities of ArrayTrack™ with SAS Scientific Discovery Solutions (SDS) to provide the research community more comprehensive bioinformatics capabilities than each solution does alone.

PI: Tong, Weida, Ph.D.

Development of Liver Toxicity Knowledge Base (LTKB) to Empower the FDA Review Process (E0721501)

Responsible Division: Systems
Toxicology

Collaborating Divisions: Z-Tech

Objectives:

- 2) Liver Ontology (LO)–To develop a Liver Ontology (LO) that characterizes liver pathology and toxicity
- 3) Gene-Expression Data–The primary data collected for this project will be existing gene-expression data. Other types of data such as data from proteomics, metabonomics, and genotyping studies (including GWAS) will be considered as the project progresses

- 4) Text Mining–To conduct text mining on >13 million abstracts in *PubMed* and other public resources with an emphasis on liver-related data
- 5) Known Data–To assemble the substantial knowledge available in public domains on liver toxicity, including genes/proteins (e.g., signatures and biomarkers), pathways/networks, and chemicals/drugs in such a way that it can be integrated with other information in LTKB and effectively mined
- 6) Experiment–To conduct gene-expression studies on well-understood and characterized hepatic and nonhepatic compounds
- 4) LTKB–To establish liver toxicity-related regulatory networks and genes/proteins-pathways-chemicals-disease associations

PI: Tong, Weida, Ph.D.

Development and Refinement of the FDA Genomic Tool, ArrayTrack™, for Advancing Pharmacogenomics and Personalized Medicine in the Context of the FDA's Critical Path Initiative (S00671)

Responsible Division: Systems
Toxicology

Objectives:

- 1) To receive data from CDER drug review offices and use ArrayTrack™ to analyze data and send results back to CDER collaborators
- 2) To develop new modules in ArrayTrack™ to review proteomics

and metabolomics data and data from genome-wide association studies

- 3) To develop ArrayTrack™ modules to allow electronic data submission in the VGDS/VXDS program

PI: Tong, Weida, Ph.D.

Empowering the FDA Review Process on Clinical and Preclinical Data Through Electronic Data Submission (S00699)

Responsible Division: Systems Toxicology

Collaborating Divisions: Z-Tech

Objectives:

To conduct a pilot study to demonstrate the review process of clinical and preclinical data with electronic data submission and provide a framework for sponsors and FDA to develop expertise, tools, and processes appropriate for regulatory implementation of e-submission

FY 2008 Publications

Publication is an essential component of research. All documents authored by NCTR investigators must undergo the NCTR Document Review and Approval Process, which consists of the review, clearance, and approval by the Center Director prior to submitting the publication to a journal. The list below identifies the NCTR-approved publications that were **accepted or published in journals in FY 2008**.

1. Abdolpour, F., Shahverdi, A.R., Rafii, F., Fazeli, M. and Amini, M. 2007. Effects of piperitone on the antimicrobial activity of nitrofurantoin and on nitrofurantoin metabolism by *Enterobacter cloacae*. *Pharmaceutical Biology*. 45(3):230-234.
Responsible Division: Microbiology
2. Ali, S.F. and Sharma, H.S. 2008. Acute Administration of 3,4-methylenedioxymethamphetamine induces profound hyperthermia, blood-brain barrier disruption, brain edema formation, and cell injury. *Annals of the New York Academy of Sciences*. 1139:242-258.
Responsible Division: Neurotoxicology
3. Antunes, A.M., Duarte, M.P., Santos, P.P., Gamboa Da Costa, G., Heinze, T.M., Beland, F.A. and Marques, M.M. 2008. Synthesis and characterization of DNA adducts from the HIV reverse transcriptase inhibitor nevirapine. *Chemical Research in Toxicology*. 21:1443-1456.
Responsible Division: Biochemical Toxicology
4. Arikawa, E., Sun, Y., Wang, J., Zhou, Q., Ning, B., Dial, S.L., Guo, L. and Yang, J. 2008. Cross-platform comparison of SYBR green real-time PCR with TaqMan PCR microarrays and other gene expression measurement technologies evaluated in the MAQC study. *BMC Genomics*. 9:328.
Responsible Division: Systems Toxicology
Co-Author Division: Personalized Nutrition and Medicine
5. Arlt, V.M., Stiborova, M., Gamboa Da Costa, G., Farmer, P.B. and Phillips, D.H. 2008. Metabolic activation of benzo[a]pyrene *in vitro* by hepatic cytochrome P450 contrasts with detoxification *in vivo*: Experiments with hepatic cytochrome P450 reductase null mice. *Carcinogenesis*. 29:656-65.
Responsible Division: Biochemical Toxicology
6. Axume, J. 2007. The MTHFR 677TT genotype and folate intake interact to lower global leukocyte DNA methylation in young Mexican American women. *Nutrition Research*. 27(1):1365-1317.
Responsible Division: Biochemical Toxicology
7. Baek, S., Moon, H., Ahn, H., Kodell, R.L., Lin, C. and Chen, J.J. 2008. Identifying high-dimensional biomarkers for personalized medicine via variable importance ranking. *Journal of Biopharmaceutical Statistics*. 18:1-16.
Responsible Division: Personalized Nutrition and Medicine

8. Bagnyukova, T.V., Tryndyak, V.P. and Pogribny, I.P. 2008. Induction of oxidative stress and DNA damage in rat brain by a folate/methyl-deficient diet. *Brain Research*. 1237:44-51.
Responsible Division: Biochemical Toxicology
9. Bagnyukova, T.V., Tryndyak, V.P., Montgomery, B.A., Churchwell, M.I., Karpf, A.R., Muskhelishvili, L., Beland, F.A. and Pogribny, I.P. 2008. Genetic and epigenetic changes in rat preneoplastic liver tissue induced by 2-acetylaminofluorene. *Carcinogenesis*. 29(3):638-46.
Responsible Division: Biochemical Toxicology
Co-Author Division: Toxicologic Pathology Associates
10. Bagnyukova, T.V., Tryndyak, V.P., Muskhelishvili, L., Ross, S., Beland, F.A. and Pogribny, I.P. 2008. Epigenetic downregulation of the suppressor of cytokine signaling 1 (Socs1) gene is associated with the STAT3 activation and development of hepatocellular carcinoma induced by methyl-deficiency in rats. *Cell Cycle*. 7(20):3202-3210.
Responsible Division: Biochemical Toxicology
Co-Author Division: Toxicologic Pathology Associates
11. Beger, R., Buzatu, D.A. and Wilkes, J.G., Quantitative Spectrometric Data-Activity Relationships (QSDAR) models of endocrine disruptor binding activities. *CRC Press*. (Book Chapter).
Responsible Division: Systems Toxicology
12. Beger, R., Holland, R.D., Sun, J., Schnackenberg, L., Devarajan, P., Dent, C. and Portilla, D. 2008. Metabolomics of acute kidney injury in children after cardiac surgery. *Pediatric Nephrology*. 23(6):977-984.
Responsible Division: Systems Toxicology
13. Boctor, S.Y., Wang, C. and Ferguson, S.A. 2008. Neonatal PCP or ketamine treatment modifies preweaning behaviors in Sprague-Dawley rats. *Toxicological Sciences*. 106(1):172-179.
Responsible Division: Neurotoxicology
14. Bowyer, J.F., Latendresse, J.R., Delongchamp, R.R., Muskhelishvili, L., Warbritton, A.R., Thomas, M., Tareke, E., McDaniel, L.P. and Doerge, D.R. 2008. The effects of subchronic acrylamide exposure on gene expression, neurochemistry, hormones, and histopathology in the hypothalamus-pituitary-thyroid axis of male Fischer 344 rats. *Toxicology and Applied Pharmacology*. 230(2):208-215.
Responsible Division: Biochemical Toxicology
Co-Author Divisions: Personalized Nutrition and Medicine, Toxicologic Pathology Associates
15. Cederroth, C.R., Vinciguerra, M., Kuhne, F., Doerge, D.R., Foti, M., Rohner-Jeanrenaud, F., Vassalli, J. and Nef, S. 2008. Dietary phytoestrogens activate AMP-activated protein kinase with improvement in lipid and glucose metabolism. *Diabetes*. 57(5):1176-1185.
Responsible Division: Biochemical Toxicology

16. Cerniglia, C.E. and Sutherland, J.B., Degradation of polycyclic aromatic hydrocarbons by fungi. *Microbiology of Hydrocarbons, Oils, Lipids, and Derived Compounds* in (T. McGenity) Springer-Verlag, Heidelberg. (Book Chapter).
Responsible Division: Microbiology
17. Chan, P.C. and Fu, P.P. 2007. Toxicity of Panax ginseng - An herbal medicine and dietary supplement. *Journal of Food and Drug Analysis*. 15:416-27.
Responsible Division: Biochemical Toxicology
18. Chang, C., Zou, W. and Chen, J.J. 2008. A new method for gene identification in comparative genomic analysis. *Journal of Data Science*. 6:415-427.
Responsible Division: Personalized Nutrition and Medicine
Co-Author Division: Microbiology
19. Chen, D., Chen, D., Schell, M.J., Chen, J.J., Fulp, W.J., Eschrich, S. and Yeatman, T. 2008. A predictive risk probability approach for microarray data with survival as the endpoint. *Journal of Biopharmaceutical Statistics*. 18(5):841-852.
Responsible Division: Personalized Nutrition and Medicine
20. Chen, H., Xu, H., Kweon, O., Chen, S. and Cerniglia, C.E. 2008. Functional role of the Trp-105 of an *Enterococcus faecalis* azoreductase (AzoA) as resolved by structural and mutational analysis. *Microbiology*. 154:2659-2667.
Responsible Division: Microbiology
Co-Author Division: Office of Research
21. Chen, J.J., Chen, Y. and Cheng, K.F. 2007. Statistics for risk assessment of chemical carcinogens. *Journal of Environmental Science and Health, Part C, Environmental Carcinogenesis and Ecotoxicology Reviews*. 25:281-312.
Responsible Division: Personalized Nutrition and Medicine
22. Chen, J.J., Hsueh, H., Delongchamp, R.R., Lin, C.J. and Tsai, C. 2007. Reproducibility of microarray data: A further analysis of microarray quality control data. *BMC Bioinformatics*. 8:412.
Responsible Division: Personalized Nutrition and Medicine
23. Chen, T. 2007. Genotoxicity of aristolochic acid, a review. *Journal of Food and Drug Analysis*. 15(4):387-394. (Book Chapter).
Responsible Division: Genetic and Reproductive Toxicology
24. Chen, T., Heflich, R.H., Moore, M. and Harris, A.J. 2008. Genetic toxicology. *American Industrial Hygiene Association*. Chap 13:136-154. (Book Chapter).
Responsible Division: Genetic and Reproductive Toxicology
Co-Author Division: Office of Research
25. Delongchamp, R.R., Velasco-gonzalez, C., Desai, V.G., Lee, T. and Fuscoe, J. 2008. Designing toxicogenomics studies that use DNA array technology. *Bioinformatics and Biology Insights*. 2:323-334.
Responsible Division: Personalized Nutrition and Medicine
Co-Author Division: Systems Toxicology

26. Desai, V.G., Lee, T., Delongchamp, R.R., Leakey, J.E., Lewis, S.M., Lee, F.W., Moland, C.L., Branham, W.S. and Fuscoe, J. 2008. Nucleoside reverse transcriptase inhibitors-(NRTIs) induced expression profile of mitochondrial genes in the mouse liver. *Mitochondrion*. 8:181-195.
Responsible Division: Systems Toxicology
Co-Author Division: Office of Research, Personalized Nutrition and Medicine
27. Desai, V.G., Lee, T., Moland, C.L., Branham, W.S., Von Tungeln, L.S., Beland, F.A. and Fuscoe, J. 2008. Effect of short-term exposure to zidovudine (AZT) on the expression of mitochondria-related genes in skeletal muscle of neonatal mice. *Mitochondrion*. 9(1):9-16.
Responsible Division: Systems Toxicology
Co-Author Divisions: Biochemical Toxicology, Personalized Nutrition and Medicine
28. Doerge, D.R., Young, J.F., Chen, J.J., Dinovi, M. and Henry, S.H. 2008. Using diet exposure and physiologically based pharmacokinetic/pharmacodynamic modeling in human risk extrapolations for acrylamide toxicity. *Journal of Agricultural and Food Chemistry*. 56(15):6031-6038.
Responsible Division: Biochemical Toxicology
Co-Author Division: Personalized Nutrition and Medicine
29. Duffy, P.H., Lewis, S.M., Mayhugh, M.A., Trotter, R.W., Thorn, B.T. and Feuers, R.J. 2008. Non-neoplastic pathology in male Sprague-Dawley rats fed the AIN-93M purified diet at *ad libitum* and dietary restricted intakes. *Nutrition Research*. 28(3):179-189.
Responsible Division: Genetic and Reproductive Toxicology
Co-Author Divisions: Biochemical Toxicology, Toxicologic Pathology Associates, Systems Toxicology, Bionetics Site Management, Z-Tech Corporation
30. Elkins, C., Munoz, M.E., Mullis, L. and Hart, M.E. 2008. *Lactobacillus*-mediated inhibition of clinical toxic syndrome *Staphylococcus aureus* strains and its relation to acid and peroxide production. *Anaerobe*. 14(5):261-267.
Responsible Division: Microbiology
31. Fan, X., Wang, Y., Perkins, R.G., Cheng, Y. and Tong, W., Feature fusion for chromatographic fingerprinting and its application to quality control of botanical drugs. *European Journal of Pharmaceutics and Biopharmaceutics*.
Responsible Division: Systems Toxicology
Co-Author Division: Personalized Nutrition and Medicine
32. Fang, H., Harris, S.C., Su, Z., Chen, M., Qian, F., Shi, L., Perkins, R.G. and Tong, W., ArrayTrack-An FDA and public genomic tool. *Methods of Functional Analysis (Pathways and Networks)*. The Humana Press, Inc., Totowa, NJ. (Book Chapter).
Responsible Division: Systems Toxicology
Primary Author Division: Z-Tech Corporation

33. Fang, H., Perkins, R.G., Shi, L., Sheehan, D.M. and Tong, W., The FDA's Endocrine Disruptor Knowledge Base (EDKB)—lessons learned in QSAR modeling and applications. *Devillers-Endocrine Disruption Modelling*. Taylor and Francis Group, LLC, Boca Raton, FL. (Book Chapter).
Responsible Division: Systems Toxicology
Primary Author Division: Z-Tech Corporation
34. Fang, J., McGarrity, L.J. and Beland, F.A. 2008. Interference of cell cycle progression by zidovudine and lamivudine in NIH 3T3 cells. *Mutagenesis*. 24(2):133-141.
Responsible Division: Biochemical Toxicology
Co-Author Divisions: Genetic and Reproductive Toxicology
35. Ferguson, S.A., Gopee, N., Paule, M.G. and Howard, P. 2009. Female mini-pig performance of temporal response differentiation, incremental repeated acquisition, and progressive ratio operant tasks. *Behavioural Processes*. 80(1):28-34.
Responsible Division: Neurotoxicology
Co-Author Divisions: Biochemical Toxicology
36. Fu, P.P. 2007. Quality assurance and safety of herbal dietary supplements. *Journal of Food and Drug Analysis*. 15:333-334.
Responsible Division: Biochemical Toxicology
37. Fu, P.P., Xia, Q., Chou, M.W. and Lin, G. 2007. Detection, hepatotoxicity, and tumorigenicity of pyrrolizidine alkaloids in Chinese herbal plants and herbal dietary supplements. *Journal of Food and Drug Analysis*. 15:400-415.
Responsible Division: Biochemical Toxicology
38. Fu, P.P., Xia, Q., Guo, L., Yu, H. and Chan, P.C. 2008. Toxicity of kava kava. *Journal of Environmental Health. Part C. Environmental Carcinogenesis and Ecotoxicology Reviews*. 26(1):89-112.
Responsible Division: Biochemical Toxicology
Co-Author Division: Systems Toxicology
39. Fuscoe, J. 2008. Impact of systems toxicology on the 3Rs. *Alternatives to Animal Testing and Experimentation*. 14:629-632.
Responsible Division: Systems Toxicology
40. Gamboa Da Costa, G., Phillips, D.H. and Arlt, V.M. 2008. Gene expression profiles modulated by the human carcinogen aristolochic acid I in human cancer cells and their dependence on TP53. *Toxicology and Applied Pharmacology*. 232:86-98.
Responsible Division: Biochemical Toxicology
Co-Author Division: Genetic and Reproductive Toxicology
41. Gerecke, D.R., Chen, M., Isukapalli, S., Chang, Y., Tong, W., Welsh, W.J., Androulakis, I.P. and Georgopoulos, P. 2009. Differential gene expression profiling of mouse skin after sulfur mustard exposure: extended time response and inhibitor effect. *Toxicology and Applied Pharmacology*. 234(2):156-165.
Responsible Division: Systems Toxicology
Co-Author Division: Personalized Nutrition and Medicine

42. González-Cortés, C., Salinas-Lara, C., Gómez-López, M.A., Tena-Suck M.L., Pérez-De La Cruz, V., Rembao-Bojórquez, D., Pedraza-Chaverrí, J., Gómez-Ruiz, C., Galván-Arzate, S., Ali, S.F., Santamaría, A. 2008. Iron porphyrinate FeTTPS reduces brain cell damage in intrastrially rats lesioned by quinolinate. *Journal of Neurochemistry*. 30(6):510-519.
Responsible Division: Neurotoxicology
43. Hong, H., Su, Z., Ge, W., Shi, L., Perkins, R.G., Fang, H., Xu, Z., Chen, J.J., Han, T., Kaput, J., Fuscoe, J. and Tong, W. 2008. Assessing batch effects of genotype calling algorithm BRLMM for the Affymetrix GeneChip Human Mapping 500K array set using 270 HapMap samples. *BMC Bioinformatics*. 9(Suppl 9):S17.
Responsible Division: Systems Toxicology
Co-Author Divisions: Personalized Nutrition and Medicine, Z-Tech Corporation
44. Hong, H., Xie, Q., Ge, W., Qian, F., Fang, H., Shi, L., Su, Z., Perkins, R.G. and Tong, W. 2008. Mold2, molecular descriptors from 2D structures for chemoinformatics and toxicoinformatics. *Journal of Chemical Information and Modeling*. 48:1337-1344.
Responsible Division: Systems Toxicology
Co-Author Division: Z-Tech Corporation
45. Hotchkiss, C.E., Bishop, M.E., Dertinger, S.D., Slikker, W., Moore, M. and MacGregor, J.T. 2008. Flow cytometric analysis of micronuclei in peripheral blood reticulocytes IV: An index of chromosomal damage in the rhesus monkey (*Macaca mulatta*). *Toxicological Sciences*. 102:352-358.
Responsible Division: Bionetics Animal Husbandry/Diet Preparation
Co-Author Divisions: Office of the Director, Genetic and Reproductive Toxicology
46. Jones, R.C., Deck, J., Edmondson, R.D. and Hart, M.E. 2008. Relative quantitative comparisons of the extracellular protein profiles of *Staphylococcus aureus* UAMS-1 and its sarA, agr, and sarA agr regulatory mutants using one-dimensional polyacrylamide gel electrophoresis and nanocapillary liquid chromatography coupled with tandem mass spectrometry. *Journal of Bacteriology*. 190(15):5265-5278.
Responsible Division: Microbiology
Co-Author Division: Systems Toxicology
47. Ju, Y.H., Doerge, D.R., Hartman, J.A., Kwak, J. and Helferich, W.G. 2008. Dietary genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) *in vivo*. *Carcinogenesis*. 29(11):2162-2168.
Responsible Division: Biochemical Toxicology
48. Jung, C.M., Heinze, T.M., Deck, J., Strakosha, R. and Sutherland, J.B. 2008. Transformation of N-phenylpiperazine by mixed cultures from a municipal wastewater treatment plant. *Applied and Environmental Microbiology*. 74(19):6147-6150.
Responsible Division: Microbiology
Co-Author Divisions: Office of Research, Biochemical Toxicology

49. Jung, C.M., Heinze, T.M., Strakosha, R., Elkins, C. and Sutherland, J.B. 2009. Acetylation of fluoroquinolone antimicrobial agents by an *Escherichia coli* strain isolated from a municipal wastewater treatment plant. *Journal of Applied Microbiology*. 106:564:571.
Responsible Division: Microbiology
Co-Author Divisions: Office of Research, Biochemical Toxicology
50. Kaldhone, P., Nayak, R.R., Lynne, A.M., Mcdermott, P.F., Logue, C.M., Foley, S.L. and David, D.E. 2008. Characterization of *Salmonella enterica* serovar Heidelberg from turkey-associated sources. *Applied and Environmental Microbiology*. 74(16):5038-5046.
Responsible Division: Microbiology
51. Kaput, J. 2008. Nutrigenomics research for personalized nutrition and medicine. *Current Opinions in Biotechnology*. 19:110-120.
Responsible Division: Personalized Nutrition and Medicine
52. Kim, S., Kweon, O. and Cerniglia, C.E. Degradation of polycyclic aromatic hydrocarbons by *Mycobacterium* strains. *Springer Science and Business Media* in (Kenneth N. Timmis) Springer Science and Business Media, Heidelberg, Germany. (Book Chapter).
Responsible Division: Microbiology
53. Kim, S., Kweon, O., Jones, R.C., Edmondson, R.D. and Cerniglia, C.E. 2008. Genomic analysis of polycyclic aromatic hydrocarbon degradation in *Mycobacterium vanbaalenii* PYR-1. *Biodegradation*. 19:859-881.
Responsible Division: Microbiology
Co-Author Division: Systems Toxicology
54. Kim, Y. and Cerniglia, C.E. An overview of the fate and effects of antimicrobials used in aquaculture. *Veterinary Pharmaceuticals in the Environment* in (K. Henderson and J. Coats) American Chemical Society. (Book Chapter).
Responsible Division: Microbiology
55. Kovalchuk, O., Tryndyak, V.P., Chekhun, V.F. and Pogribny, I.P. 2008. Involvement of microRNA-451 in resistance of the MCF-7 breast cancer cells to chemotherapeutic drug doxorubicin. *Molecular Cancer Therapeutics*. 7(7):2152-2159.
Responsible Division: Biochemical Toxicology
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Responsible Division: Microbiology
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Responsible Division: Microbiology
Co-Author Division: Personalized Nutrition and Medicine

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Responsible Division: Personalized Nutrition and Medicine
Co-Author Division: Systems Toxicology
59. Li, S., Lin, G., Fu, P.P., Chan, C., Jiang, Z. and Zhao, Z. 2008. Identification of five hepatotoxic pyrrolizidine alkaloids in a commonly used traditional Chinese medicinal herb, *Herba Senecionis scandentis* (Qianliguang). *Rapid Communication in Mass Spectrometry*. 22(4):591-602.
Responsible Division: Biochemical Toxicology
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Responsible Division: Personalized Nutrition and Medicine
Co-Author Divisions: Office of the Director, Biochemical Toxicology, Genetic and Reproductive Toxicology, Office of Information Technology
61. Malejka-Giganti, D., Parkin, D.R., Decker, R.W., Niehans, G.A., Bliss, R., Churchwell, M.I. and Beland, F.A. 2008. Tumorigenicity and genotoxicity of an environmental pollutant 2,7-dinitrofluorene after systemic administration at a low dose level to female rats. *International Journal of Cancer*. 122(9):1958-1965.
Responsible Division: Biochemical Toxicology
62. Manjanatha, M., Shelton, S.D., Dobrovolsky, V.N., Shaddock, J.G., McGarrity, L.J., Doerge, D.R., Twaddle, N.C., Lin, Chien-Ju, Chen, J.J., Mattison, D. and Morris, S.M. 2008. Pharmacokinetics, dose-range, and mutagenicity studies of methylphenidate hydrochloride in B6C3F1 mice. *Environmental and Molecular Mutagenesis*. 49(8):585-593.
Responsible Division: Genetic and Reproductive Toxicology
Co-Author Divisions: Biochemical Toxicology, Personalized Nutrition and Medicine
63. Mckinney, M.D., Moon, S., Kulesh, D.A., Larsen, T. and Schoepp, R.J. 2009. Detection of viral RNA from paraffin-embedded tissues after prolonged formalin fixation. *Journal of Clinical Virology*. 44:39-42.
Responsible Division: Biochemical Toxicology
64. Mei, N., Manjanatha, M., Azuma, M., McDaniel, L.P., Dial, S.L., Tseng, J., Liao, W. and Guo, L. 2008. Liver gene expression profile of mice treated with acrylamide in drinking water. *Proceedings of the 2008 International Conference on Bioinformatics and Computational Biology*. I:131-137.
Responsible Division: Genetic and Reproductive Toxicology
Co-Author Divisions: Biochemical Toxicology, Systems Toxicology

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Co-Author Division: Systems Toxicology
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Glossary of Acronyms and Abbreviations

This glossary is provided to assist you in interpreting acronyms, abbreviations, and phrases you encounter while reading this publication. This is not meant to take the place of standard language or scientific dictionaries, which should be referred to if any short form of a scientific term does not appear in this glossary. Also, you may refer to the Index of Key Terms, located at the end of this publication as a quick reference to locate other occurrences of a specific term.

Acronym/ Abbreviation	Name
3-NPA	3-nitropropionic acid or methamphetamine
3-NT	3-nitrotyrosine
3TC	lamivudine
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care, International
AALAS	American Association for Laboratory Animal Science
ACB-PCR	allele competitive blocker-polymerase chain reaction
ACLAM	American College of Laboratory Animal Medicine
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
AFMID	arylformamidase
AIDS	acquired immunodeficiency syndrome
ASCP	American Society for Clinical Pathology
A β	amyloid β -peptide
AZT	zidovudine or azidothymidine
CBER	Center for Biologics Evaluation and Research, FDA
CBPR	community-based participatory research
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research, FDA
cDNA	complementary DNA
CDRH	Center for Devices and Radiological Health, FDA
CFSAN	Center for Food Safety and Applied Nutrition, FDA
CLSI	Clinical and Laboratory Standards Institute
CMAR	Certified Managers of Animal Resources
CNS	central nervous system
CRADA	Cooperative Research and Development Agreement
CVM	Center for Veterinary Medicine, FDA

Acronym/ Abbreviation	Name
CYP	cytochrome
DBS	deep-brain stimulation
DEHP	di-(2-ethylhexyl)phthalate
DGRT	Division of Genetic and Reproductive Toxicology
DHHS	Department of Health and Human Services
DHP	6,7-dihydro-7-hydroxy-1-hydroxymethyl-5H-pyrrolizine
DNMT	DNA methyltransferase
DPNM	Division of Personalized Nutrition and Medicine
DVS	Division of Veterinary Services
EDTA	ethylene-diamine-tetra-acetic acid
ENU	<i>N</i> -ethyl- <i>N</i> -nitrosourea
EPA	Environmental Protection Agency
ERIC	enterobacterial repetitive intergenic consensus
FDA	Food and Drug Administration
FDA Centers	Center for Biologics Evaluation and Research (CBER) Center for Devices and Radiological Health (CDRH) Center for Drug Evaluation and Research (CDER) Center for Food Safety and Applied Nutrition (CFSAN) Center for Veterinary Medicine (CVM) National Center for Toxicological Research (NCTR) Office of Regulatory Affairs (ORA)
GABA	gamma-aminobutyric acid
GD	gestational day
GGT	guanine guanine thymidine
GST	glutathione S-transferase
GTT	guanine thymidine thymidine
GWAS	Genome-Wide Association Study
HF/LC	high fat/low carbohydrate
HIV	human immunodeficiency virus
HMA	human microbiota-associated
HPLC	high-performance liquid chromatography
IACUC	Institutional Animal Care and Use Committee
IAG	Interagency Agreement
IHC	immunohistochemical
<i>in silico</i>	modeled on a computer
<i>in situ</i>	in place; localized and confined to one area

Acronym/ Abbreviation	Name
<i>in vitro</i>	in animal models
<i>in vivo</i>	in cell cultures
IPRG	Interdisciplinary Pharmacogenomics Review Group
ISH	<i>in situ</i> hybridization
LC/MS	liquid chromatography-mass spectrometry
LCM	laser capture microdissection
LNPA	lymph node proliferation assay
MALT	mucosal-associated lymphoid tissues
MAQC	MicroArray Quality Control
MF	mutant fraction
MLA	mouse lymphoma assay
MPP+	1-methyl-4-phenylpyridinium
MPTP	1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRS	magnetic resonance spectroscopy
MS	mass spectrometry
NCFST	National Center for Food Safety and Technology
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research, FDA
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NMDA	n-methyl-d-aspartate
NMR	nuclear magnetic resonance
nNOS	neuronal nitric oxide synthase
NP	<i>p</i> -nonylphenol
NTP	National Toxicology Program
ORA	Office of Regulatory Affairs, FDA
OTB	operant test battery
OWH	Office of Women's Health, FDA
PAH	polycyclic aromatic hydrocarbon
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction

Acronym/ Abbreviation	Name
PD	Parkinson's Disease
PET	positive emission tomography
PFGE	pulsed-field gel electrophoresis
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-f]pyridine
PI	Principal Investigator
PIG-A	phosphatidylinositol glycan anchor biosynthesis, class A
PPAR	peroxisome proliferator-activated receptor
QDOT	quantum dot
REP-PCR	repetitive extragenic palindromic-PCR
RLS	Restless Leg Syndrome
RNA	ribonucleic acid
ROS	reactive-oxygen species
RT-PCR	reverse transcriptase-polymerase chain reaction
SAB	Science Advisory Board
SAGE	Serial Analysis of Gene Expression
SDS	SAS Scientific Discovery Solutions
SKH-1	species of mouse
SLE	systemic lupus erythematosus (lupus)
SNP	single nucleotide polymorphism
SSL	simulated-solar light
TCR	T-cell receptor
TiO ₂	titanium dioxide
TK	thymidine kinase
TSST-1	Toxic-shock syndrome toxin-1
UGT1A1	UDP-glucuronosyltransferase 1A1
USDA	United States Department of Agriculture
UV, UVA, or UVB	ultraviolet (A or B indicates the region)
VEC	vaginal-epithelial cells
VGDS	Voluntary Genomic Data Submission
VISION	VGDS/IPRG Status and Information ON-line

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